COLORECTAL SURGERY AND ADHESIONS

Martijn W.J. Stommel

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Introduction

Colorectal cancer surgery and adhesions

Surgical trauma, invasive pathogens, and tumors are all known triggers for an inflammatory reaction of the peritoneum, thus, can potentially cause adhesion formation. Not surprisingly, colorectal surgery is associated with high risk of adhesions and adhesion-related complications.[1-3] In colorectal resection, large wound surfaces are created on the lateral abdominal wall, retroperitoneum, and occasionally, the omentum and pelvic organs loosening attachments and dividing mesentery. Colorectal surgery always involves some degree of contamination of the peritoneal cavity, even in elective surgery. In addition, a substantial number of colorectal surgical procedures are performed because of a perforation: this enhances the risk of various levels of contamination. Colorectal cancer is the main indication for colorectal surgery, with approximately 7,000 colon and 2,500 rectum operations for primary colorectal cancer performed annually in the Netherlands.[4]

Adhesion-related complications have a significant adverse effect on patients' health, and lead to an increased workload in clinical practice. After an abdominal surgical procedure, many patients develop an episode of small bowel obstruction, which is usually caused by adhesions. This often requires emergency surgery with adhesiolysis.[5-7] Adhesiolysis in elective repeat surgery is associated with inadvertent bowel injury, longer operating time, and conversion to an open approach in laparoscopic procedures.[8, 9] Other consequences of adhesions include decreased pregnancy rates, increased fertility treatments, and chronic abdominal pain.[10]

Adhesions and laparoscopy

The majority of studies on adhesion formation and adhesion-related complications focus on open surgery. The question of the extent of the adhesion problem in laparoscopic surgery arises. Laparoscopy limits parietal peritoneal injury due to the use of smaller incisions. In laparoscopy, tissue manipulation is minimized (e.g. no retractors, no gloves), blood loss is less, and the closed peritoneal cavity prohibits the introduction of large swabs, which are factors that are known stimuli in adhesion formation.[11, 12] In two nationwide surveys in the Netherlands, both gynecologists and surgeons were found to believe that laparoscopic technique reduces adhesions.[13, 14] However, the evidence that supports this assumption is limited to a few comparative studies that have reported lower composite adhesion scores after laparoscopic colorectal surgery in small series.[15-18] More studies have been published on the incidence of adhesion-related clinical endpoints after laparoscopic colorectal surgery. In recent years, two large, population-based register studies, showed a lower risk for adhesion-related readmissions and small bowel obstruction after laparoscopic colorectal surgery, compared to open colorectal surgery.[19, 20] A meta-analysis of non-randomized studies showed that laparoscopy, in general, seems to have a lower incidence of small bowel obstruction.[21] Although it seems plausible that these advantages of laparoscopic surgery could be the result of less adhesion

formation, reliable data on differences in incidence of adhesions after laparoscopic or open surgery is lacking.

Even in modern, minimally invasive surgery, adhesion formation remains relevant, because adhesions are a risk factor for conversion from minimally invasive to open colectomy.[22] Laparoscopic conversion itself is associated with more postoperative complications, and even with worse overall survival rates.[23, 24]

Adhesions and oncologic resection

Patients undergoing colorectal cancer surgery frequently have a history of abdominal surgery, and consequential intra-abdominal adhesions.[8] If adhesions surround the tumor, identifying structures and avoiding iatrogenic injury might be difficult and could compromise the resection. As a result, the extent of colorectal resection may be jeopardized, with possibly smaller or even incomplete resection margins. Narrow resection margins have been identified as risk factors for poor lymph node harvest, alongside patient-related factors, such as male gender and increasing age.[25] A lower number of lymph nodes harvested results in under-staging and subsequent under-treatment of patients.[26] More extensive nodal dissection is associated with improved survival, although the causal relation between the number of nodes and outcome remains a topic of debate.[26, 27] Influence of repeat surgery on oncological parameters has scarcely been reported. Two retrospective studies showed no difference in number of harvested lymph nodes and resection margin between patients with- or without previous abdominal surgery.[28, 29] Both studies comprised low numbers of patients and both reported the overall mean number of lymph nodes harvested at less than 10. This low number of lymph nodes harvested possibly reflects inadequate surgical resection or inadequate quality of histopathological examination of the specimens that could confound conclusions on the impact of previous abdominal surgery. Importantly, these studies provided no information on adhesion formation as a cause of poorer oncologic resection quality. If pre-existing adhesions in colorectal surgery jeopardize oncologic resection, this would seriously further increase the burden of adhesions, with possibly the same negative effect in oncologic reoperation for (recurrent) liver metastases, local recurrence, or peritoneal metastases.[30, 31]

Adhesion prevention

The ultimate aim of adhesion preventive measures and products is to increase the number of patients without any adhesion formation to 100 percent, as no adhesions means no adhesion related complications. With good surgical techniques (e.g. minimization of surgical trauma, avoiding introduction of foreign materials), adhesions can be reduced, but not prevented.[11] Adhesion barriers

seem necessary to increase the number of patients without any adhesion after both open- and laparoscopic surgery. In open colorectal surgery, incidence of adhesions can be reduced by 45% through the use of an adhesion barrier.[32] Today, more than 65% of colorectal resections are performed by laparoscopic approach.[4] The effect of an adhesion barrier on the incidence of adhesions after laparoscopic colorectal surgery is unknown; limited data is present of reduction in extent and severity of adhesions. Accurate data on incidence of adhesions after laparoscopic surgery is required for optimal design of studies on the effect of adhesion barriers in laparoscopic procedures.

Existing cost-effectiveness calculations of adhesion barriers are based on open surgery and do not suffice for current colorectal practice with over 50 percent laparoscopic procedures.[33] Many colorectal surgeons question cost-effectiveness of barriers in laparoscopic surgery beforehand. New data, for example, that derived from modeling and prospective studies of adhesion barriers, will give better insight into the question of whether or not adhesion barriers are safe and (cost-) effective in laparoscopic colorectal surgery.

Aims of this thesis

- To assess the incidence of postoperative adhesions after both open and minimally invasive colorectal surgery.
- To assess the influence of previous abdominal surgery on clinical and histopathological outcome of colorectal cancer surgery.
- To study the possible gain for adhesion barriers in colorectal surgery in the minimally invasive era, and if it is expedient.

Outline of the thesis

In **Chapter 2** the response of the peritoneum involved in intraperitoneal inflammation, adhesion formation, sepsis, and tumor growth are discussed. Regardless of the specific process, injury to the peritoneal mesothelial cells results in activation of an inflammatory response to heal the wound. The inflammatory reaction comprises of four interacting pathways: immunological, humoral, coagulation, and neurological. Colorectal cancer surgery is associated with all mentioned noxa to the peritoneum and peritoneal cavity.

In **Chapter 3** the impact of adhesiolysis on the clinical outcomes of colorectal surgery and histopathological results of colorectal cancer surgery are determined. A total of 249 colorectal procedures were selected from the earlier prospective cohort study of adhesiolysis-related problems. The incidence of bowel injury, morbidity, costs, and the histopathology between patients undergoing

elective colorectal surgery with or without adhesiolysis is also compared.

In **Chapter 4,** the evaluation of the effect of prior abdominal surgery on the outcome of colorectal cancer surgery is described. The large Dutch Surgical Colorectal Cancer Audit (DSCA) prospective database of more than 25, 000 colorectal cancer patients was used. Outcome of primary colorectal cancer resection was compared between patients with and patients without prior abdominal surgery. Primary outcome measures were: number of lymph nodes harvested; circumferential rectal resection margin (CRM); CRM positivity; and completeness of resection in colon cancer. Secondary outcome measures were postoperative complications and 30-day mortality.

Laparoscopic technique is generally thought to decrease the impact of colorectal resection, with regard to post-operative recovery, but also with regard to adhesion formation. To date, there is no sound evidence to substantiate this assertion.

In **Chapter 5,** the incidence of adhesions after laparoscopic versus open colorectal cancer resection is investigated. A multicenter prospective study was performed, in which adhesions were scored during 151 liver resections for colorectal metastases. Comparison was made between prior laparoscopic and open colorectal resection on the incidence of adhesions to the ventral abdominal wall around the site of the original incision. Secondary outcomes were incidence of any adhesions, extent and severity of adhesions, as well as morbidity related to adhesions or adhesiolysis.

Since minimally invasive techniques are not expected to completely prevent adhesion formation, evidence regarding efficacy and safety of adhesion barriers continue to be of interest in the laparoscopic era.

In **Chapter 6,** adhesion barriers that are approved for clinical use by the Food and Drug Administration (FDA) are systematically reviewed and meta-analyzed. Outcome measures were: reoperation for adhesive small bowel obstruction; serious adverse events; overall incidence of adhesions; operation time; small bowel obstruction by any cause; site-specific incidence of adhesions; and adhesion score.

Despite the efficacy of adhesion barriers and the burden of adhesions, adhesion barriers are seldom applied. In a nationwide survey in The Netherlands, only 13.4% of surgeons indicated to have used any adhesion barrier in the previous year.[13] The survey revealed that surgeons do not believe in the efficacy of anti-adhesive agents, lack clarity about when to use the barriers, and think that the costs do not outweigh the benefits for the patient.

In **Chapter 7,** the expediency of the use of adhesion barriers in colorectal surgery is determined. A decision-tree model was developed to determine health costs of treatment strategies with- and without the use of adhesion barriers, for both open and laparoscopic operative techniques. Probabilities were derived from recently published literature. Only direct healthcare costs were included.

In **Chapter 8,** the study protocol is described for a randomized controlled trial to assess efficacy and safety of C-Qur™ Film adhesion barrier. This study aimed to add to the evidence on the use of adhesion barriers in open and laparoscopic colorectal surgery. The primary endpoint was incidence of adhesions at repeat surgery, since it is believed to be the most valuable surrogate endpoint for clinically relevant adhesion prevention. When complete adhesion reduction in a patient is accomplished, small bowel obstruction and adhesiolysis at repeat surgery are not likely to occur.
In **Chapter 9** a summary of the thesis and a general discussion are presented.

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2

Response to pathological processes in the peritoneal cavity - Sepsis, tumours, adhesions, and ascites

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Abstract

The peritoneum is one of the commonest sites for pathological processes in pediatric surgery. Its response to pathological processes is characterized by an inflammatory reaction with specific pathways depending on the type of injury or peritoneal process involved. This review discusses the current understanding of peritoneal inflammation, adhesion formation, intra-abdominal sepsis, peritoneal metastasis, and ascites and briefly reviews new therapeutic strategies to treat or prevent these pathological entities. Recent studies have improved the understanding of peritoneal responses, resulting in possible new targets for prevention and therapy.

Introduction

The peritoneal cavity is a confined space between the parietal peritoneum lining the abdominal wall, the retroperitoneum, and the visceral peritoneum covering the abdominal organs. Its total surface area is almost equal to the body surface area of the skin.[1] The peritoneum is a serous membrane of mesodermal origin, consisting of a monolayer of flat mesothelial cells anchored to the basement membrane. The subjacent connective tissue consists mainly of loose collagen fibers, including fibroblasts, blood and lymphatic vessels, as well as nerve fibers. The mesothelial cells play an active role in the physiological function as well as in pathological processes of the peritoneum. The peritoneal cavity contains less than 100 ml of serous fluid, an ultra-filtrate of plasma, which together with hyaluronan and a surfactant, produced by mesothelial cells, facilitates frictionless movement of the abdominal organs.[2] The peritoneum acts as a bidirectional semipermeable membrane. The peritoneal mesothelial cells are interrupted by intermesothelial gaps (stomata of von Recklinghausen), which adapt to pathological conditions by retraction of the cell margins in response to pathological stimuli and in relation with diaphragmatic movements. At these stomata the peritoneal cavity is directly exposed to the extracellular matrix.[3] The action of the diaphragm generates a cephalad flow of peritoneal fluid through the stomata.[4] Under normal circumstances, approximately one-third of the peritoneal fluid drains through the diaphragmatic stomata into the main thoracic lymphatic ducts, the remainder exits through the parietal peritoneum.

The peritoneal defense mechanism can be triggered by various types of pathological processes “injuring” the peritoneum. Apart from (surgical) trauma, injury can be caused by invasive pathogens and tumor. The peritoneum responds to injury with an inflammatory reaction. This inflammatory reaction comprises four interacting pathways: immunological, humoral, coagulation, and neurological. In this article, we aim to give a comprehensive overview of the response to pathological processes in the peritoneal cavity.

General peritoneal response to injury

Injury of the peritoneum, whether surgical, inflammatory, or ischemic, causes a complex inflammatory reaction. This response has an integral role in wound healing and tissue repair to heal any sustained damage. The disruption of the cellular membrane, through apoptosis or necrosis, causes a release of intracellular molecules such as DNA, ATP, and IL-1α in the extracellular space.[5–7] These have been named as Damage-Associated Molecular Pattern molecules (DAMPs), but the mechanisms by which they generate an inflammatory response are not fully understood. The DAMPs induce a local cascade through activating receptors on mesothelial and local inflammatory cells. The mesothelial and local inflammatory cells produce chemoattractants (IL-8 and MCP-1), cytokines (TNF α, IL-1β, and IL-6), and growth factors (TGF β, IGF-1, and PDGF), which result in neutrophil extravasation which infiltrate the damaged area.[8] Mast cells are abundantly present around bowel mucosa and are believed to play an important role in the inflammatory response of the peritoneum by inducing vasodilation through release of histamine. They can also be activated by DAMPs and activate several local immunological and endothelial cells and nerve fibers.[9] Neutrophils persist at the injured site for 1–2 days and are followed by monocytes recruited in the same manner; these differentiate into macrophages which contribute to the inflammatory reaction. The primary injury of the peritoneum not only leaves a denuded area with damaged mesothelial cells but also causes bleeding and extravasation of plasma proteins. Coagulation is up-regulated through the expression of tissue factor (TF) by macrophages and mesothelial cells. Interaction of TF with plasma proteins and thrombocytes forms a transient fibrinous matrix. The formation of an extensive fibrinous matrix is possible because the balance between coagulation and fibrinolysis is disturbed. The fibrinogen split products are known to promote pleural mesothelial proliferation, this might also be the case with peritoneal mesothelial cells.[10] Fibrinolysis, however, is decreased because there is an up-regulation of plasminogen activator inhibitor 1 (PAI-1) and a down-regulation of tissue-type plasminogen activator (t-PA). There is increasing evidence that inflammation and coagulation significantly affect each other. Coagulation is induced by inflammatory cytokines, while the coagulation-induced modulation of inflammatory activity is driven by specific cell receptors on inflammatory cells and endothelial cells.[7] Moreover, thrombocytes play their part in inflammation through storage and release of the pro- and anti-inflammatory factors TGF β and IL-1.[5]

The neurological pathway of the inflammatory response of the peritoneum is activated by IL-1 binding to paraganglia cells. The “inflammatory reflex” is formed by signaling through afferent fibers of the vagus nerve to parasympathetic regions in the brainstem, leading to the release of neuropeptides from efferent

nerve fibers and a resultant feedback on inflammation.[11] Different neuropeptides can lead to either anti-inflammatory (e.g., acetylcholine) or proinflammatory (e.g., substance P) effects on

inflammation.

While in the past resolution of inflammation has always been seen as a passive process, the discovery of locally acting mediators (pro-resolving mediators) has changed this view.[12] These proresolving mediators are produced via transcellular biosynthesis (i.e., between neutrophils and thrombocytes) and down-regulate the inflammatory reaction.

Adhesion formation

Healing of the injured peritoneum can result in the formation of peritoneal adhesions. As mentioned, injury of the peritoneum leads to a denuded surface with submesothelial damage evoking an inflammatory response. Simultaneously the coagulation cascade is activated and fibrin deposited at the site. A serosanguinous exudate rich in inflammatory cells, fibronectin, glycosaminoglycans, and proteoglycans is secreted through increased vascular permeability. This results in fibrin deposits that form an adhesion between two formerly unconnected structures. Under normal circumstances, these fibrin deposits are degraded by fibrinolysis. This process of fibrinolysis is driven by the enzyme plasmin produced by macrophages and mesothelial cells. Plasmin is derived from its inactive substrate plasminogen by tissue-type plasminogen activator (t-PA) and urokinase-like plasminogen activator (u-PA). In its turn, t-PA is inhibited in its reaction by plasminogen activator inhibitor 1 (PAI-1) to keep the balance. However, peritoneal trauma leads to the absence of adequate fibrinolytic activity of the mesothelium and a mismatch in the fibrinolytic balance in favor of the persistence of fibrin clots.[13] Neighboring organs or the abdominal wall ma y adhere, generating a fibrin bridge between the attached tissues.[14] Under the actions of various cytokines, these fibrin bands are transformed into granulation tissue by the ingrowth of capillaries and fibroblasts and subsequently converted into permanent, collagenous, and highly organized tissue containing nerve fibers and vessels.

Adhesions frequently cause long-term complications after abdominal and pelvic surgery. After pediatric abdominal surgery, the incidence of adhesive small bowel obstruction can be as high as 15.6%, for example, after treatment of gastroschisis and omphalocele in neonates.[15,16] Other important clinical consequences of adhesions include infertility, chronic abdominal pain, malabsorption, and technical difficulties at reoperation. Many pharmacological methods and barriers have been used for adhesion prevention but only few have been proven to be successful. Prevention of adherence of adjacent structures by keeping them apart seems most efficacious. In a recent systematic review, the efficacy and safety of the four adhesion barriers approved for use in Europe and the USA were evaluated, showing evidence that membranes of oxidized regenerated cellulose and hyaluronate carboxymethylcellulose reduce adhesion formation.[17] Moreover, there is evidence that hyaluronate carboxymethylcellulose reduces the number of reoperations for adhesive small

bowel obstruction. Evidence for efficacy on other clinically critical outcomes is lacking. Of the liquid adhesion barriers that are available in the market, icodextrin 4% solution is the most widely used. There is, however, limited evidence for the beneficial effect of icodextrin on the incidence of small bowel obstruction or other adhesion-related complications.[17,18]

An understanding of the pathological processes enables the modulation of the peritoneal environment and fibrinolytic capacity, which seems to harbor a therapeutic opportunity to prevent postsurgical adhesion formation. Intraperitoneal treatment with recombinant human plasminogen activator (rPA) was effective in preventing postoperative adhesion formation in experimental studies.[13] A pilot study in humans, however, showed no reduction of adhesions.[19] Since there was no measurable elevation of plasma t-PA level in the treatment group, this negative result was ascribed to too small a dosage.

An interesting option to potentially combine anti-inflammatory, anti-coagulatory, and profibrinolytic properties is the use of statins. Beside their cholesterol-lowering capacity, there is accumulating evidence that statins effectively lower plasma levels of CRP, have potent anti-inflammatory properties, and are effective stimulators of fibrinolytic activity by increasing t-PA and lowering PAI-1.[20,21] Also, the use of an angiotensin-II receptor blocker has potential efficacy in adhesion prevention through decreasing TGF β. The intraperitoneal administration of these agents alone and combined effectively reduced postsurgical adhesions in mice.[22] However, no data on efficacy in humans are available yet. Another potentially viable therapeutic target is substance P (a specific proinflammatory neuropeptide).[23] The effects associated with substance P are increasing inflammatory cytokine mRNA expression, stimulating angiogenesis, and proliferation of fibroblasts. This is mainly mediated through binding to neurokinin-1 receptor. Binding to the neurokinin-1 receptor can be inhibited through intraperitoneal administration of a neurokinin-1 receptor antagonist. In rats, interference with the actions of substance P with this antagonist showed early effects on the mRNA expression of several key mediators of adhesiogenesis.[24]

Intra-abdominal infection, abscess formation, and peritonitis

Intra-abdominal infection encompasses all forms of bacterial peritonitis, intra-abdominal abscesses, and infections of intra-abdominal organs. Perforation of a hollow organ is the leading cause of intra-abdominal infection, followed by postoperative peritonitis, ischemic damage of the bowel wall, infection of intra-abdominal organs, and translocation in nonbacterial peritonitis.[25]

Within minutes of bacterial invasion, a substantial proportion of the bacteria are absorbed from the peritoneal cavity through the stomata of von Recklinghausen in the diaphragmatic peritoneum and into the thoracic lymphatics.[26] At the same time, the bacteria activate the local response triggered by reaction of mesothelial cells and peritoneal macrophages, very similar to the response

induced by sterile stimuli.[27] Chemoattractants, produced by mesothelial cells and local inflammatory cells, induce the recruitment of phagocytes (neutrophils and later macrophages), transmigrating from peritoneal capillaries to the mesothelial surface. Dilation of peritoneal blood vessels results in enhanced permeability, peritoneal edema, and the formation of protein-rich peritoneal exudates.[28] The local defense mechanism is able to localize and control the bacterial invasion through the formation of fibrinous adhesions trapping microbes and promoting local effector mechanisms to phagocytose them.[29] The omentum contributes to the overall localization process. The mesothelial cell layer of the omentum encloses two distinct types of tissue: an adipose-rich area and a thin translucent membranous area.[30] The adipose-rich area contains omental milky spots, consisting mainly of inflammatory cells. The translucent area has a net-like structure with multiple fenestrations, and its function is associated with regulating fluid transport. The fenestrations also facilitate adhesion of the omentum to damaged or inflamed organs, giving it motile properties. Once localized to the site of contamination, the omentum acts to absorb microbes and contaminants through its stomata and secretes phagocytes through the milky spots. The omentum promotes healing via the local expression of growth factors and the stimulation of angiogenic activity.[31] An abscess forms when this localizing defense mechanism fails to completely clear the bacterial contamination. Such abscesses consist of bacteria, neutrophils, and necrotic debris walled off by a fibrinous or fibrous capsule termed pyogenic membrane. When viable bacteria are entrapped in the abscess wall or in the center, they cannot be reached by phagocytes and antibiotic therapy. This can result in bacterial proliferation[32] and, if overwhelmed, can lead to a systemic inflammatory response syndrome through the release of pro-inflammatory mediators (e.g., TNF α and IL-1) into the systemic circulation.[33]

The cornerstones of successful therapy in intra-abdominal infection are—source control, drainage of abscesses, and appropriate antibiotics. Very early antibiotic intervention is effective in reducing mortality in sepsis. Empirical use of antibiotics is often necessary when confronted by a sick patient and should be reevaluated by local resistance surveillance.[34] The choice of the empirical antibiotic regimen should cover the intestinal flora, aerobes, and anaerobes. Examples of broad-spectrum antimicrobial regimens for pediatric patients with complicated intra-abdominal infection are an aminoglycoside-based regimen, a carbapenem (imipenem, meropenem, or ertapenem), a β-lactam/β-lactamase inhibitor combination (piperacillin–tazobactam or ticarcillin–clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole.[35]

After surgically eliminating the source of abdominal infection in patients with severe abdominal sepsis, open abdomen should be avoided, since it leads to higher mortality.[36] An open abdomen is defined as a situation where the skin and fascia cannot be closed after laparotomy and the viscera

are exposed, needing temporary closure or coverage techniques.[37] The only indication for open abdominal management is abdominal compartment syndrome, although even in this circumstance, temporary closure without tension is recommended. Planned re-laparotomy is not recommended and results in a higher mortality, a longer ICU and hospital stay, and higher costs[34,36] when compared with an "on-demand" strategy of surgical re-exporation.

Ascites

Ascites is a pathological state where an excess of fluid is accumulated within the peritoneal cavity. In approximately 80% of cases in adults, ascites is caused by hepatic cirrhosis. Other common causes include malignancy in 10% and heart failure in 3%.[38] Hepatic disorders are the most common cause of ascites in infants and children.[39]

Three pathophysiologic processes contribute to the development of ascites in patients with cirrhotic liver disease: portal hypertension, vasodilation, and hyperaldosteronism. During the development of hepatic cirrhosis, the sinusoidal endothelial cells of the intra-hepatic microcirculation fail to function, resulting in aberrant paracrine signaling. This process causes inflammation, fibrosis, and impaired vasomotor control, leading to increased intra-hepatic vascular resistance and portal hypertension.[40] Additionally, sinusoidal cells are highly permeable to albumin, making lymph formation dependent on hydrostatic forces alone, which are increased due to portal hypertension. A systemic effect of portal hypertension is vasodilation through increased nitric oxide production and hydrostatic pressure of the splanchnic circulation, leading to more fluid extravasation into the peritoneum. Furthermore, systemic vasodilatation results in relative hypovolemia and stimulates the renin–angiotensin–aldosterone system.[41] Increased antidiuretic hormone secretion induces water retention. While angiotensin normally promotes vasoconstriction, in the presence of hepatic cirrhosis, this effect is dampened.[42] If a patient develops hypoalbuminemia, a lower intra-vascular osmotic pressure exacerbates this process.

An extensive summary of the different treatments for ascites due to cirrhotic liver disease goes beyond the scope of this review. In short, the intake of sodium should be restricted, and in most patients, addition of a diuretic is necessary. The most effective diuretic is spironolactone but a combination with furosemide might be required.[43,44] Paracentesis is a safe and effective treatment in the management of diuretic-resistant ascites.[45] If more than 5 l of fluid will be removed through paracentesis, intravenous albumin has been shown to improve survival.[46] A transjugular intra-hepatic portosystemic shunt has shown to improve

transplant-free survival in comparison to large-volume paracentesis.[47] Liver transplantation is a viable treatment in patients who develop diuretic-resistant ascites and early referral to a transplant center should be standard care.

In the presence of peritoneal malignancy, ascites has a completely different etiology. Malignant ascites develops because of a mismatch between filtration and drainage in the peritoneal cavity. In patients with peritoneal carcinomatosis, the cross-sectional area of microvessels that line the peritoneal cavity is increased.[48] Furthermore, due to the secretion of Vascular Endothelial Growth Factor (VEGF) by tumor cells, the permeability of microvessels is increased,[49] leading to an increased accumulation of protein-rich fluid in the peritoneal cavity. This shifts the oncotic pressure gradient further in the direction of the peritoneum. Impaired drainage from the peritoneum can also be caused by tumor cells blocking the peritoneal stomata, but this is a less important mechanism.[50]

Due to the differences in etiology between malignant and cirrhotic ascites, diuretics are less effective in the treatment of malignant ascites. However, patients with extensive liver metastases might benefit from a diuretic.[51] Intraperitoneal chemotherapeutics, corticosteroids, cytokines, and a VEGF inhibitor have been reported to improve the control of ascites.[52–55] A randomized clinical trial using intraperitoneal administration of a monoclonal antibody, Catumaxomab, showed longer paracentesis-free survival and improved palliation in comparison to paracentesis alone.[56] Aflibercept, a VEGF inhibitor given intravenously, was evaluated in a phase 2, double-blinded, randomized, placebo-controlled study also showed longer paracentesis-free survival, although this did not lead to an improved overall survival.[57]

Complete resection of peritoneal metastasis is often not possible in patients with malignant ascites. Furthermore, the duration of postoperative recovery is comparable to the median overall survival time, making this patient category often considered ineligible for cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy (HIPEC).[58] Therefore, a laparoscopic approach with limited adhesiolysis and no cytoreductive surgery combined with HIPEC has been advocated. Due to its minimally invasive nature, this procedure has shown to be safe, and promising results with regard to palliation and overall survival have been reported.[59,60]

Peritoneal metastasis

Peritoneal metastasis is a common route for gastrointestinal malignancies, including appendiceal, colorectal, gastric, and pancreatic cancers. It is the primary metastatic route for ovarian malignancies. Peritoneal carcinomatosis is associated with a poor prognosis, irrespective of the primary origin of the tumor.[8,27] The process of intraperitoneal tumor dissemination differs from hematologic metastasis where tumor cells need to enter and exit the circulation and penetrate tissues. Peritoneal dissemination occurs in gastrointestinal malignancies when tumor cells exfoliate from the primary tumor after it has invaded the visceral peritoneum or in the case of a perforation of the gastrointestinal tract.[11] After dissemination into the peritoneum, tumor cells must prevent apoptosis and evade peritoneal clearance through the lymphatic system. This requires tumor cells to attach to the disrupted mesothelial surface or the exposed extracellular matrix (ECM) or at the stomata of von Recklinghausen for further disease progression. Tumor cells may adhere to the surface of mesothelial cells through various receptors[61–63] but show a predilection of adhering to type 1 collagen of the ECM.[64,65] The ECM is, therefore, the initial site of metastasis.[66] Surgical injury of the peritoneum exposes the ECM and damages the mesothelial cell layer.[67] Additionally, interactions between immune, mesothelial, and tumor cells create an inflammatory environment that causes the mesothelium to retract, exposing more of the ECM. Furthermore, inflammatory cytokines up-regulate mesothelial cell surface receptors enabling the attachment of tumor cells[68,69] and therefore increase metastatic spread. Tumor cells have the ability to assemble into multicellular aggregates, named spheroids, through direct cell–cell attachments.[70] When formed into spheroids, tumor cells have increased resistance against anoikis and chemotherapeutics.[71] Additionally, spheroid formation is associated with more invasive tumors.[72] Targeting spheroid formation by attenuating the contractile abilities of tumor cells might be an important treatment modality and is an area of extensive research.[73] The presence of ascites in patients with advanced ovarian cancer decreases their life expectancy when compared with patients who present without ascites in similar advanced ovarian cancer.[74] Malignant ascites contains multiple growth factors and cytokines,[75–77] which enhance resistance against chemotherapeutic agents[78] and promote spheroid formation of tumor cells.[79] Increased amounts of fibrinogen and fibrin found in ascites may lead to the assemblage of tumor deposits that can become vascularized because of the presence of

angiogenic growth factors.[80] Notably, heparin-binding epidermal growth factor (HB-EGF) has been shown to contribute to disease progression in ovarian cancer patients.[81] A small study reported promising results with an inhibitor of HB-EGF.[82]

The cornerstone in the treatment of peritoneal carcinomatosis, in the absence of other systemic metastasis, is complete cytoreductive surgery and HIPEC. Although associated with considerable morbidity and mortality, it has shown to improve overall survival. An important prognostic factor for survival is complete macroscopic tumor resection.[83,84]

Conclusion

The inflammatory reaction of the peritoneum forms an essential part of the physiopathology of abscess formation, adhesion formation, malignant ascites, and peritoneal metastasis. Specific pathways and interactions depend on the type of injury to the peritoneum. An increased understanding of these pathological processes has yielded potential targets for new therapies.

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3

Impact of Adhesiolysis on Outcome of Colorectal Surgery

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Abstract

Background/Aims: Adhesiolysis is a frequent part of colorectal surgery, potentially impeding the operation and causing inadvertent bowel injury. Such difficulties might compromise convalescence and oncological quality of resection. The aim of this prospective cohort study was to assess the impact of adhesiolysis on clinical outcomes and histopathological results in colorectal surgery.

Methods: Colorectal procedures were selected from a prospective cohort study of adhesiolysis-related problems. We compared the incidence of bowel injury, morbidity, costs, and the histopathology between patients undergoing elective colorectal surgery with or without adhesiolysis.

Results: Two hundred and forty nine colorectal surgeries were analysed. Adhesiolysis was required in 59.0%. The mean adhesiolysis time was 28 min. In the adhesiolysis group, enterotomies occurred in 6.1% and seromuscular injuries in 27.2% compared to 0 and 6.9% respectively in the non-adhesiolysis group ($p = 0.012$ and $p < 0.001$). In patients requiring adhesiolysis, 29.9% had major surgery-related complications (MSRC) compared to 15.7% without adhesiolysis ($p = 0.007$). There were no statistically significant differences regarding inpatient costs and resection margin or number of harvested lymph nodes.

Conclusions: Adhesiolysis during colorectal surgery is related to an increased incidence of iatrogenic bowel injuries and MSRC. Despite the technical challenges associated with adhesiolysis, good histopathological results were obtained in oncological resections.

Introduction

Adhesion formation is the most frequent cause of long-term complications following abdominal surgery. Complications of adhesions comprise small bowel obstruction and difficulties during reoperation.[1,2] In a recent prospective series of major abdominal or pelvic surgeries, more than half of laparotomies required adhesiolysis, resulting in extension of operative time, 10% inadvertent bowel injury and more postoperative surgical complications.[3] The need for adhesiolysis was particularly high in colorectal and abdominal wall surgery, with colorectal surgery being most frequently performed in this series.

Despite the fact that colorectal surgery has been the focus of adhesion formation and prevention research in the past decades[4–7], the precise impact of adhesiolysis and related organ injury on the outcome of colorectal surgery has not been investigated. Knowledge of adhesion-related morbidity is needed to inform patients properly and to take adhesiolysis-related risks into account in the operative decisionmaking. In addition, proper data on adhesiolysis time and the socioeconomic burden are helpful for operative room management and reimbursement policy.

In colorectal cancer surgery, technical difficulties related to adhesiolysis might also interfere with the extent and quality of the resection. Adhesions may complicate appropriate mobilization of the colon and rectum[8], thereby compromising resection margins and lymph node harvest. A lower number of lymph nodes harvested results in under-staging of tumours and subsequent under-treatment of patients.[9] A more extensive nodal dissection is associated with improved survival.[9,10] In addition to patient-related factors such as male gender and increasing age, narrow resection margins have been identified as risk factors for poor lymph node harvest.[11]

The aim of this prospective study was to demonstrate the impact of adhesiolysis on bowel injury, major surgery related complications (MSRC), hospital costs, and oncological quality of resection in a cohort of elective colorectal operations.

Methods and Materials

Study Design

This is a prospective observational study as part of the Laparotomy or Laparoscopy and Adhesions (LAPAD) study (ClinicalTrials.gov registration number NCT01236625). Detailed information on the LAPAD methods have been described previously.[3,12] The LAPAD study was designed to assess the incidence and impact of adhesiolysis on per- and postoperative complications, quality of life and hospital costs. All adult competent patients undergoing elective laparotomy or laparoscopy admitted to the surgical ward between June 1, 2008 and June 2, 2010

at the department of surgery of the Radboud University Medical Center, Nijmegen, the Netherlands, were screened for participation in the LAPAD study. The study was approved by the local Institutional Review Board and conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul).

Cohort Selection

For each patient participating in the LAPAD study, the planned and actual operative procedures were noted using the hospitals operation coding system. The indications for the procedure were defined following the International Statistical Classification of Diseases and Related Health Problems, version 10 (ICD-10). The current study group was selected by operative procedure codes related to colorectal surgery. The datasheet, indications and operative notes of all patients within this cohort were reviewed. Patients undergoing multiple procedures in the same operative session were excluded if the colorectal procedure was only a minor part of the total surgery.

Relevant patient, surgical and medical data were prospectively assessed before, during and after hospital stay and at the outpatient clinic until 6 months after discharge. At surgery, detailed information on adhesions, adhesiolysis and inadvertent organ damage was collected through direct observation by a trained researcher who did not take part in the operation.

The presence of adhesions was assessed and the location, for example, ventral abdominal wall, operative area and other parts of the abdomen, was described. At these 3 locations, adhesions were graded according to the Zühlke classification 1 filmy adhesions: easy to separate by blunt dissection; no vascularization; 2 stronger adhesions: blunt dissection possible but partly sharp dissection possible (beginning of vascularization); 3 strong adhesions: lysis possible but sharp dissection only; clear vascularization; 4 very strong adhesions: lysis possible by sharp dissection only (organ strongly attached with severe adhesions and damage of organs hardly preventable).[13] The duration of adhesiolysis was timed by stopwatch. Findings were recorded into the database real time by the researcher present in the operating theatre.

Variables

Primary outcomes were the incidence of adhesions, adhesiolysis time, the incidence of bowel defects, seromuscular injury, injuries to other organs and structures and the incidence of MSRC. Bowel defects were classified as inadvertent enterotomy or delayed diagnosed perforation (DDP). Inadvertent enterotomy was defined as any iatrogenic, unintended full thickness

bowel defect detected during operation. Pre-existing fistulas or defects created while dissecting the bowel loop that harboured the fistula were not scored as inadvertent enterotomy. DDP was defined as a bowel defect with spill of gastrointestinal content that was diagnosed postoperatively by imaging, at reoperation or at autopsy, and which could not be explained by anastomotic leakage, bowel ischemia or any other obvious cause of leakage unrelated to adhesiolysis.

Seromuscular injury was defined as injury to the serosa and muscular layers of the bowel, without visualization of the bowel lumen or spillage of bowel content. As a rule, seromuscular injuries were repaired by suturing. Other intraoperative injuries comprised injury to the spleen, liver, pancreas, urogenital structures, lung, vascular structures, or nerves.

Postoperative complications noted as MSRC were death, wound infection, anastomotic leak, fistula and abscess, pneumonia, sepsis, and haemorrhage. MSRCs were defined according to the criteria of the ICD-10, the National Nosocomial Infections Surveillance System, the Centre for Disease Control and prevention, or according to the decision of the senior surgical staff of the department.

Secondary outcomes were other morbidity, oncological outcome and hospital costs including total operative time, blood loss, recovery unit stay, hospital stay, intensive care unit (ICU) admission, ICU stay, parenteral feeding, tube feeding, incidence of emergency reoperations, and incidence of readmission to the hospital within 30 days after discharge.

Costs analysis included only the direct hospital costs: operation costs, ward stay, ICU stay, extra charges for parenteral and tube feeding, postoperative diagnostics, reoperation costs and blood products. Costs calculations were performed using the guidelines for cost analysis of the Dutch College of Health Insurance Companies using a top-down approach.[14] Operation costs were calculated based on total anaesthesia time using operation room costs of $1,390 per hour including personnel, material and overhead costs. Total costs for the surgical ward and ICU were $661 and 2,289 per day respectively and included basic nutrition costs. Advanced methods of parenteral and tube feedings were considered extra nutritional costs. Diagnostics and reoperation costs were calculated using the 2004 price list for medical procedures by the Dutch College of Health Insurance Companies. Medication costs and blood products costs were calculated according to the standardized price list of the Dutch College of Health Insurance Companies updated for June 2008.[15]

Oncological outcome was analysed in the subgroups of patients who had undergone surgery for colon or rectal cancer. The number of harvested lymph nodes, completeness of resection and distance from the bowel resection margin plain in colon resections and circumferential resection margin (CRM) in rectal resections, were extracted from the pathology reports. In

our pathology department, a standardized report for colorectal cancer is used following the checklist recommended by the Dataset for colorectal cancer (2nd edition) of the Royal College of Pathologists and the Dutch National Guidelines for Colorectal Cancer Surgery.[16,17] Baseline demographics included gender, age, body mass index, smoking status, alcohol use disorders identification test alcohol abuse index[18], abdominal operations in history, number of laparotomies in history, number of laparoscopies in history, generalized peritonitis in history, ASA classification, P-possum score, revised cardiac risk index, operative severity, surgical approach (open or laparoscopic) and level of surgical experience (consultant or resident).

Statistical Methods

Baseline characteristics, preoperative complications, postoperative morbidity and costs were compared between the patients that underwent adhesiolysis and the group that did not undergo adhesiolysis. In the subgroup of patients that underwent a resection of colorectal cancer, we compared the number of harvested lymph nodes, completeness of resection and distance from the bowel resection plain in colon resections and CRM in rectal resections, between patients with and without adhesiolysis.

Adhesions form during the healing process of most often surgical, but also inflammatory, injury of the peritoneum.[19] In order to achieve more homogeneity, the subgroup of patients that underwent adhesiolysis after prior abdominal surgery was analysed and preoperative complications and postoperative morbidity were compared with patients without adhesiolysis.

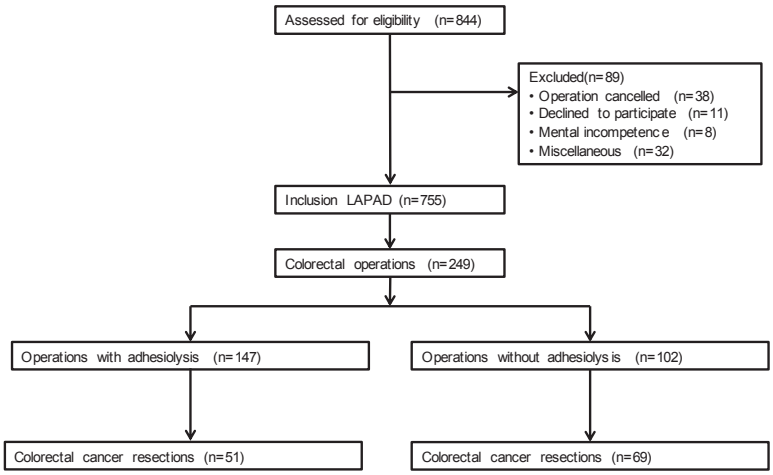
Univariate comparisons were performed using linear regression for continuous and logistic regression for dichotomous data. Correlation between incidence of enterotomy and severity of adhesions (Zühlke classification) was assessed using Fisher's exact test. Continuous data are expressed as mean with SD and dichotomous data as number with percentages. In composite outcomes, statistical results are presented for both the composite outcome and the individual components of the composite. Costs are presented as mean cost with 95% CI and expressed in US dollars. Dichotomous data were tested using univariate and multivariate regression. In multivariate regression, results were corrected for differences in baseline with $p < 0.10$, except for a history of abdominal surgery and history of generalized peritonitis. Prior abdominal surgery and peritonitis were considered pathogenic for adhesion formation and were not expected to have further independent adverse effects on treatment outcomes.

Statistical comparison of costs was performed by t test on the logistically transformed values of the costs to reduce the impact of outliers. All outcomes were assessed per operation and analysed according to intention-to-treat, unless otherwise stated.

There was only minimal missing data; thus, we excluded cases with missing data per analysis. We

used SPSS® for Windows version 20.0 software (SPSS®, Chicago, Ill., USA) for statistical analysis. $p < 0.05$ was considered significant.

Figure 1: Flow diagram of the included operations.



Results

Cohort and Baseline Comparison

Eight hundred and forty four consecutive elective operations were screened for inclusion in the LAPAD study. Flow diagram of included operations is shown in figure 1. Two hundred and fifty five operations had one or more colorectal surgery codes. By reviewing the datasheets and operative notes, 6 operations were excluded because the colorectal procedure performed was only a minor part of the total surgery. Two hundred and forty nine patients who underwent a colorectal operation were included in this study. One hundred and twenty were oncological resections (fig. 1). Data on classification of adhesions were missing in 3/249 operations (1.2%). There were no further missing data.

Adhesions were present in 151 of 249 patients (60.6%). One hundred and thirty eight patients had a history of intra-abdominal surgery of whom 115 (83.3%) had adhesions, 111 patients had no prior abdominal surgery of whom 36 (32.4%) had abdominal adhesions. Adhesions to the incisional scar of a previous operation were found in 104/138 (75.4%) patients with prior

abdominal surgery. In 120 of 151 (79.5%) patients, adhesions were present at the operative area and in 86 of 151 (57.0%), adhesions were found at other parts of the abdomen.

Adhesiolysis was performed in 147 patients. Median Zühlke score of the adhesions was 3 (range 1–4) at the incision scar and at the operative area of a previous operation, and 2.5 (range 1–4) at other parts of the abdomen. Mean adhesiolysis time was 28.0 min (±32.3) and median 15 min (1–177).

Table 1 shows the baseline data for the groups with and without adhesiolysis. Patients in the adhesiolysis group were younger ($p = 0.002$) and had more abdominal surgery ($p < 0.001$) and generalized peritonitis ($p < 0.001$). More patients in the adhesiolysis group were operated by a consultant and not a registrar ($p = 0.003$). Indications for surgery were equally divided, except for restoration of bowel continuity ($p < 0.001$). There were no other significant differences in baseline characteristics.

Impact of Adhesiolysis on Peroperative Complications

Twelve inadvertent enterotomies (median 1, range 1–3) occurred in 9 out of 147 (6.1%) patients in the adhesiolysis group and none in the non-adhesiolysis group ($p = 0.012$; table 2). In all, 12 enterotomies occurred only in patients with a history of a previous laparotomy, in 1 out of 50 (2.0%) after one and in 8/63 (12.7%) after 2 or more prior open abdominal surgeries ($p = 0.015$). In operations complicated by an inadvertent enterotomy, the median highest Zühlke score was 4 (range 3–4).

Inadvertent injury to the seromuscular layer occurred in 40 (27.2%) procedures with adhesiolysis compared to 7 (6.9%) without adhesiolysis ($p < 0.001$).

DDP occurred in 3 patients in the adhesiolysis group and in none of the patients in the non-adhesiolysis group. DDP occurred after an operation with 1 enterotomy and 5 seromuscular injuries, after an operation with 1 seromuscular injury and an operation without enterotomy or seromuscular injury. DDP occurred in 2 patients with no history of abdominal surgery and 1 patient with a previous laparotomy.

Other organs were injured in 9 (6.1%) patients (vascular structures n = 4, liver n = 2, spleen n = 1, ureter n = 1, bladder n = 1) in the adhesiolysis group compared to 2 (2.0%; spleen n = 1, vascular structures n = 1) in the nonadhesiolysis group ($p = 0.23$).

Table 1: Baseline comparison between operations with and without adhesiolysis

	Adhesiolysis (n= 147)	No adhesiolysis (n=102)	p value
Demographics			
Male	68 (46.3)	59 (57.8)	0.072
Female	79 (53.7)	43 (42.2)	
Age*	56.4 ± 16.4	62.3 ± 13.8	0.002
BMI*	24.9 ± 4.2	25.4 ± 4.2	0.28
Smoking status			
Non smoker	49 (33.3)	42 (41.2)	0.33
Previous-smoker	66 (44.9)	44 (43.1)	
Smoker	32 (21.8)	16 (15.7)	
Alcohol abuse			
Low risk	141	93	0.28
Moderate risk	4	5	
High risk	2	4	
Surgical history			
Abdominal surgery in history			
Yes	113 (76.9)	23 (22.5)	< 0.001
No	34 (23.1)	79 (77.5)	
Laparotomies in history†	1 (0-11)	0 (0-2)	< 0.001
Laparoscopies in history†	0 (0-2)	0 (0-1)	0.011
Generalized peritonitis in history			
Yes	23 (15.6)	0	< 0.001
No	124 (84.4)	102 (100.0)	
Preoperative risk assessment			
ASA classification			
I	28 (19.0)	12 (11.8)	0.37
II	87 (59.2)	67 (65.7)	
III	31 (21.1)	23 (22.6)	
IV	1 (0.7)	0 (0)	
P-possum Score*	6.4 ± 10.7	6.1 ± 6.7	0.80
RCRI Index			
2	123 (83.7)	78 (76.5)	0.35
3	18 (12.2)	17 (16.7)	
4	6 (4.1)	7 (6.9)	
Operative severity			
Moderate	1 (0.7)	2 (1.9)	0.41
Large	115 (78.2)	74 (72.5)	
Major	31 (21.1)	26 (25.5)	
Operation technique			
Laparoscopic surgery	15 (10.2)	18 (17.6)	0.088
Open surgery	132 (89.8)	84 (82.4)	
Operation type			
Right colectomy	37 (25.2)	31 (30.4)	0.36
Sigmoid or rectal resection	52 (35.4)	47 (46.1)	0.090
Subtotal or proctocolectomy	21 (14.3)	11 (10.8)	0.42
Other colectomy	5(3.4)	7 (6.9)	0.21
Restoration of continuity	25 (17.0)	1 (1.0)	<0.001
End colostomy	7 (4.8)	5 (4.9)	1.0
Surgical experience			
Surgeon	98 (66.7)	53 (52.0)	0.003
Resident	49 (33.3)	49 (48.0)	

Values are mean ± SD, median (range) or n (%). BMI = body mass index; ASA = American Society of Anesthesiologists; RCRI = revised cardiac risk index.

Table 2: Peroperative complications and MSRC compared between operations with and without adhesiolysis

	Adhesiolysis (n=147)	No adhesiolysis (n=102)	Crude OR	P value	Adjusted OR*	Adjusted P value*
Peroperative complications						
Enterotomy	9 (6.1)	0	NA	0.012	NA	NA
Seromuscular injury	40 (27.2)	7 (6.9)	5.1 (2.2 – 11.9)	< 0.001	5.3 (2.1 – 13.1)	< 0.001
Other organ injury	9 (6.1)	2 (2.0)	3.3 (0.69 – 15.4)	0.14	2.7 (0.54 – 13.6)	0.23
Delayed Diagnosed	3 (2.0)	0	NA	0.27	NA	NA
Perforation						
MSRC's						
Death	6 (4.1)	2 (2.0)	2.1 (0.42 – 10.8)	0.36	2.7 (0.51 – 14.0)	0.25
Wound infection	10 (6.8)	4 (3.9)	1.8 (0.55 – 5.9)	0.34	2.0 (0.57 – 7.0)	0.28
Anastomotic leak	8 (5.4)	2 (2.0)	2.9 (0.60 – 13.8)	0.19	2.1 (0.40 – 11.0)	0.39
Fistula/abscess	7 (4.8)	2 (2.0)	2.5 (0.51 – 12.3)	0.26	1.7 (0.31 – 9.1)	0.56
Pneumonia	13 (8.8)	8 (7.8)	1.1 (0.46 – 2.9)	0.78	1.6 (0.59 – 4.4)	0.35
Sepsis	4 (2.7)	2 (2.0)	1.40 (0.25 – 7.8)	0.70	1.9 (0.31 – 11.2)	0.49
Hemorrhage	5 (3.4)	1 (1.0)	3. 6 (0.41 – 30.9)	0.25	4.1 (0.44 – 37.7)	0.22
Urinary tract infection	11 (7.5)	2 (2.0)	4.0 (0.88 – 18.7)	0.073	3.1 (0.63 – 15.3)	0.16
Any MSRC	44 (29.9)	16 (15.7)	2.3 (1.2 – 4.4)	0.011	2.6 (1.3 – 5.3)	0.007

Values are n (%). NA = Not applicable. * Adjustment for gender and age.

Impact of Adhesiolysis on Postoperative Morbidity and Costs

The incidence of total MSRCs was 44 (29.9%) in the adhesiolysis group compared to 16 (15.7%) in the nonadhesiolysis group (adjusted OR 2.6 (1.3–5.3); p = 0.007; table 2). Removing urinary tract infection as MRSC, the incidence was 36 (24.5%) and significantly higher in the adhesiolysis group compared to 15 (14.5%) in the nonadhesiolysis group (adjusted OR 2.5 (1.2–5.0); p = 0.011). There were no significant differences in the incidences of a single MSRC, also after multivariate regression.

The readmission rate within 30 days was significantly higher in the adhesiolysis group (adjusted OR 6.0 (1.7– 20.7); p = 0.005; table 3). The mean hospital stay was 11.6 ± 15.7 days in the adhesiolysis group and 9.0 ± 7.4 days in the non-adhesiolysis group (adjusted p = 0.10). There were no significant differences between the adhesiolysis and no adhesiolysis group with regard to operation time, blood loss, recovery unit stay, ICU admission and ICU stay, parenteral feeding, tube feeding and reoperations (table 3).

The inpatient costs were on average $2,355 higher in the adhesiolysis group compared to the costs in the nonadhesiolysis group. The difference did not reach statistical significance due to large variations in costs between patients (log transformed p = 0.18; table 4).

Table 3: Crude and adjusted results for morbidity outcomes compared between operations with and without adhesiolysis

	Adhesiolysis (n=147)	No adhesiolysis (n=102)	Crude OR	P value	Adjusted OR*	Adjusted P value*
Operation time (min)	201 ± 84	189 ± 80	12.3 (-8.6 to 33.3)	0.25	2.3 (-18.3 to 22.9)	0.82
Blood loss (ml)	876 ± 1044	806 ± 948	69.8 (-185.5 to 325.0)	0.60	- 104.5 (-351.9 to 143.0)	0.41
Recovery unit stay, h	5.6 ± 10.4	5.3 ± 7.6	0.35 (-2.0 to 2.7)	0.78	0.17 (-2.4 to 2.7)	0.90
Hospital stay, days	11.6 ± 15.7	9.0 ± 7.4	2.6 (-0.70 to 5.9)	0.12	2.9 (- 0.58 to 6.3)	0.10
ICU admission	24 (16.3)	17 (16.7)	0.98 (0.49 to 1.9)	0.98	1.1 (0.52 to 2.3)	0.82
ICU stay, days	1.5 ± 11.8	0.9 ± 3.6	0.89 (-0.93 to 2.7)	0.34	0.44 (-0.87 to 1.7)	0.51
Parenteral feeding	25 (17.0)	12 (11.8)	1.5 (0.73 to 3.2)	0.26	1.7 (0.74 to 3.6)	0.22
Parenteral feeding, days	10.6 ± 8.1	13.3 ± 10.6	-2.7 (-9.1 to 3.7)	0.40	-3.7 (-12.0 to 4.5)	0.36
Tube feeding	22 (15.0)	18 (17.6)	0.82 (0.42 to 1.6)	0.57	0.78 (0.37 to 1.6)	0.51
Tube feeding, days	15.5 ± 32.5	7.4 ± 6.1	7.4 (-4.3 to 19.1)	0.21	11.2 (-5.9 to 28.4)	0.19
Reoperations						
Any	28 (19.0)	12 (11.7)	1.6 (0.77 to 3.4)	0.20	1.7 (0.76 to 3.6)	0.21
Relaparotomy	22 (15.0)	10 (9.8)	1.6 (0.73 to 3.6)	0.23	1.7 (0.73 to 3.9)	0.22
Readmission within 30 days	22 (15.0)	3 (2.9)	5.8 (1.7 to 20.0)	0.005	4.9 (1.4 to 17.5)	0.015

Valueas are mean ± SD or n (%). * Adjusted for gender and age.

Table 4: Socioeconomic cost analysis compared between operations with and without adhesiolysis and compared between with or without inadvertent bowel defect in the subgroup of operations with adhesiolysis

	Adhesiolysis (n=147) mean (95% CI)	No adhesiolysis (n=102) mean (95% CI)	P value	P value (log transformed)
Operation cost	3830 (3590 to 4070)	3666 (3397 to 3954)	0.39	0.29
Ward stay	4558 (3906 to 5210)	3773 (3229 to 4317)	0.071	1.0
ICU stay	2451 (-761 to 5663)	1497 (307 to 2687)	0.59	0.83
Extra charges for parenteral/tube feeding	418 (219 to 616)	346 (130 to 563)	0.63	0.74
Medication	367 (190 to 544)	221 (151 to 291)	0.14	0.36
Diagnostics (radiology, pathology and microbiology)	269 (201 to 338)	235 (168 to 303)	0.50	0.53
Reoperations	139 (79 to 200)	79 (27 to 131)	0.14	0.14
Blood products	173 (99 to 246)	55 (20 to 91)	0.005	0.012
Total costs	12,264 (8473 to 16,055)	9909 (7731 to 12,086)	0.27	0.18

Impact of Adhesiolysis on Oncological Outcomes

One hundred and twenty patients underwent a resection for cancer, 49 for rectal and 71 for colon cancer. Twenty (41%) rectal cancer patients and 31 (44%) colon cancer patients required adhesiolysis. Baseline characteristics of these subgroups are shown in table 5. For the total group of

colorectal cancer resections, incidences of total MSRCs significantly differed between adhesiolysis and no adhesiolysis (17 (33.3%) compared to 11 (15.9%); p = 0.026; table 5). There were no significant differences in incomplete resection (circumferential), resection margin and number of harvested lymph nodes between patients with and without adhesiolysis during resection of colon or rectal cancer (table 6).

Table 5: Baseline comparison including neoadjuvant therapy between operations with and without adhesiolysis of the subgroup of colorectal resection for colorectal cancer (n = 120) and of the subgroups of operations for rectal and colon cancer

	Adhesiolysis (n=51)	**No adhesiolysis (n=69)**	**P value**	**Rectum adhesiolysis (n=20)**	**Rectum no adhesiolysis (n=29)**	**P value**	**Colon adhesiolysis (n=31)**	**Colon no adhesiolysis (n=40)**	**P value**
Gender									
Male	28 (54.9)	43 (62.3)	0.41	12 (60.0)	22 (75.9)	0.24	16 (51.6)	21 (52.5)	0.94
Female	23 (45.1)	26 (37.7)		8 (40.0)	7 (24.1)		15 (48.4)	19 (47.5)	
Age	68.8 ± 12.5	66.8 ± 9.7	0.35	63.1 ±14.4	65.9 ± 9.4	0.44	72.5 ± 9.6	67.5 ± 10.0	0.034
BMI	25.7 ± 3.7	25.4 ± 4.1	0.73	25.6 ± 3.3	25.8 ± 4.4	0.83	25.7 ± 4.0	25.1 ± 3.9	0.53
Abdominal surgery	32 (62.7)	13 (18.8)	<0.001	10 (50.0)	5 (17.2)	0.026	22 (71.0)	8 (20.0)	<0.001
SCRT-TME < 2				6 (30.0)	10 (34.5)	0.95	-	-	
SCRT-TME > 4				3 (15.0)	5 (17.2)		-	-	
CRT				8 (40.0)	11 (37.9)		-	-	
Chemotherapy				0	0		2 (6.5)	3 (7.5)	0.66
MSRC	17 (33.3)	11 (15.9)	0.026	9 (45.0)	7 (24.1)	0.13	8 (25.8)	4 (10.0)	0.078
Right	18 (35.3)	20 (29.0)	0.49	-	-		18 (58.1)	20 (50.0)	0.41
Extended right	3 (5.9)	2 (2.9)		-	-		3 (9.7)	2 (5.0)	
Left hemicolectomy	2 (3.9)	4 (5.8)		-	-		2 (6.5)	4 (10.0)	
Sigmoid resection	4 (7.8)	6 (8.7)		-	-		4 (12.9)	6 (15.0)	
Rectosigmoid	1 (2.0)	7 (10.1)		-	-		1 (3.2)	7 (17.5)	
Low anterior	13 (25.5)	12 (17.4)		12 (60.0)	12 (41.4)	0.35	1 (3.2)	0	
Abdominoperineal	8 (15.7)	16 (23.2)		8 (40.0)	16 (55.2)		0	0	
Subtotal colectomy	2 (3.9)	1 (1.4)		-	-		2 (6.5)	1 (2.5)	
Proctocolectomy	0 (0)	1 (1.4)		0 (0)	1 (3.4)		0	0	

Values are mean ± SD or n (%).

BMI = Body mass index; SCRT = short course radiotherapy; TME = total mesorectal excision; CRT = chemoradiotherapy.

Table 6: Oncological results analysis of resections in rectal colon cancer compared between operations with and without adhesiolysis.

	Rectal cancer adhesiolysis (n=20)	Rectal cancer no adhesiolysis (n=29)	Relative risk	P value		Colon cancer adhesiolysis (n=31)	Colon cancer no adhesiolysis (n=40)	P value
Incomplete resection	1 (5.0)	1 (3.4)	0.073	1.0	Incomplete resection	1 (3.2)	0	0.44
CRM (mm)	8.3 ± 6.0 (n=17)	7.6 ± 5.8 (n=21)		0.70	Margin to nearest resection plain, mm	76.1 ± 56.2 (n=26)	64.7 ± 45.7 (n=34)	0.41
Number harvested of lymph nodes	13 ± 7	12 ± 6		0.63	Number harvested of lymph nodes	15 ± 8	17 ± 10	0.42

Values are mean ± SD or n (%).

Subgroup Analysis of the Adhesiolysis Group by Cause of Adhesions

The adhesiolysis group comprised 113 patients with and 34 without prior abdominal surgery. Patients with prior abdominal surgery in the adhesiolysis group had more severe adhesions (median Zühlke score 3, range 1–4). These adhesions were mostly located under the incision of a previous operation or at the operative area (78.7 and 83.5%, respectively). Median adhesiolysis time in these patients was 18 min (1–177). The 34 patients without prior abdominal surgery mainly had a few low-grade adhesions (median Zühlke score 1, range 1–3) with a median adhesiolysis time of 5 min (range 1–93). These adhesions were mostly located at the operative area (71.4%), adjacent to a local inflammatory process or tumour.

Incidence of enterotomy due to adhesiolysis of postoperative adhesions was 9 (6.1%) and of seromuscular injury 36 (31.9%) compared to 0 and 7 (6.9%) respectively in the non-adhesiolysis group ($p = 0.004$ and $p < 0.001$). The incidence of MSRC was 30 (26.5%) in the group with adhesiolysis of postoperative adhesions compared to 16 (15.7%) in the non-adhesiolysis group ($p = 0.055$). The mean hospital stay was comparable between both groups (10.2 ± 8.4 and 9.0 ± 7.4 days [$p = 0.28$]). The readmission rate within 30 days was significantly higher in the adhesiolysis of postoperative adhesions group with 16 (14.2%) vs. 3 (2.9%) in the non-adhesiolysis group

($p = 0.004$).

Discussion

In this prospective single center study more than half of the patients undergoing colorectal surgery required some degree of adhesiolysis, predominantly in patients with previous abdominal surgery in history. Adhesiolysis led to enterotomy in 1 of 16 procedures; this ratio increased to 1 of 12 procedures in patients with postsurgical adhesions, and to 1 of 8 procedures in patients with 2 or more prior abdominal operations. Adhesiolysis doubled major surgical complications' rate and led to a higher incidence of readmission. There was a trend towards prolonged hospital stay with almost 3 days, and higher costs when adhesiolysis were needed.

This subgroup of elective colorectal operations from a prospective cohort study of 755 all types elective abdominal operations was chosen because colorectal surgery involves a large patient group and this type of surgery has been associated with adhesion-related complications.[4,20–22] Almost two-third of patients had baseline adhesions, mostly originating from previous surgery, harboring the highest risk of surgical complications when lysed. The risk is related to more dense adhesions particularly to a midline scar. Lysis of mostly filmy adhesions at the operative area adjacent to the disease process did not increase preoperative complications risk. The 28 min adhesiolysis time, the 6–8% enterotomies, the 30% occurrence of major surgical complications and 14% readmission rate are indicators of the large disease burden of postoperative adhesion formation in unselected, elective, (non)malignant colorectal surgery.[2] The 8% enterotomy rate compares favorably with the 19% of patients who incurred an enterotomy when undergoing adhesiolysis at repeat colorectal surgery in a previous retrospective analysis from our institution.[21] This higher enterotomy rate may be explained by the predominant number of patients with inflammatory bowel disease and with multiple extended resections in the previous study, necessitating more elaborated lysis of dense adhesions. Another explanation might be the stricter definition of iatrogenic bowel defects in this study, which did not include enterotomies in the proximity of a preexisting bowel fistula. The most likely explanation, however, is the increased awareness in our hospital during the last decade for adhesiolysis related complications, by surgeons taking time to carefully lyse adhesions and meticulously repair all injuries. These study results can raise awareness of other colorectal surgeons similarly taking prudence and care in operations that require adhesiolysis.

Our results are not in agreement with a large but retrospective analysis of 1,071 patients operated for colorectal cancer that, apart from delayed gastrointestinal motility, did not show a higher postoperative complication rate in patients with adhesions.[23] In that study, outcome data were based on operative and discharge reports introducing reporting bias. Operative and hospital discharge notes are inferior to concurrent tracking of adhesions and (post)operative

complications as performed in this study.[24,25] Real-time gathering of data by means of predefined scoring lists during an operation is rather unique in surgical research. It is elaborative but necessary to accurately and objectively assess operative sequelae. New technology such as Google glass or a medical data recorder may help making observation less laboursome.

This study is the first to investigate the impact of adhesiolysis on oncological quality of resection in colorectal cancer surgery. The oncological outcome parameters were not included in the study protocol but retrospectively extracted from the pathology reports. Through the use of standardized reports for colorectal cancer as recommended by the National Guidelines for Colorectal Cancer Surgery and following the Dataset for colorectal cancer (2nd edition) of the Royal College of Pathologists reliability of the pathology reports is high.[16,17] We did not find smaller resection margins or a lower number of harvested lymph nodes in patients that required adhesiolysis. This finding corresponds with results of 2 retrospective studies reporting on the impact of prior abdominal surgery on curative resection for colorectal cancer. Since abdominal surgery results in intra-abdominal adhesions in up to 90% of patients [7,26,27], prior abdominal surgery is considered a proxy of need for adhesiolysis. In patients undergoing resection of colon cancer via minilaparotomy, a similar number of harvested lymph nodes was found between patients with or without prior abdominal surgery.[28] A study in laparoscopic colorectal resection showed no significant differences in resection margins or number of harvested lymph nodes.[29] The generalizability of these 2 retrospective studies is limited since the reported numbers of lymph nodes harvested were approximately half the number we found. The number of lymph nodes retrieved from a resection specimen may be related to factors such as the extent of the resection undertaken or the use of neoadjuvant therapy, but it is likely that the accuracy of pathological examination of the specimen is most important. The quality of histopathological examination should be taken into account when reporting on differences in lymph node yield and resection margins. Unfortunately, we could only analyse oncological outcome parameters in small subgroups. Histopathological examination showed high lymph node yield, adequate margins, and low percentage incomplete resections with only minimal differences between the adhesiolysis group and the no adhesiolysis group. Despite the absence of significant differences in histopathological outcome parameters in our study, the impact of adhesiolysis on oncological outcome deserves further attention. Whether adhesiolysis impacts number of harvested lymph nodes and resection margins should be assessed in a larger cohort of colorectal cancer patients. The effect of adhesiolysis on long-term oncological outcome should be investigated as well, since long-term oncological outcome might be affected by adhesiolysis due to a higher incidence of MSRCs, which potentially delays the start of adjuvant treatment.[30]

We found a 60% incidence of adhesions in patients undergoing colorectal surgery, of whom 83% had prior abdominal, predominantly open, surgery. Since minimally invasive surgery has become the operative technique of choice for nearly all types of abdominal surgery, the incidence of adhesions and the burden might decrease in time compared to our results. A few large populationbased register studies showed a significantly lower incidence of small bowel obstruction after laparoscopic surgery compared to open abdominal surgery.[31,32] A literature review of comparative, mainly experimental, studies on adhesion formation between 1966 and 2002 showed less adhesions after laparoscopic surgery. However, laparoscopic surgery is not adhesion-free surgery.[33,34] Therefore, adhesionand adhesiolysis-related morbidity will remain a problem in the minimally invasive era. Further knowledge on incidence and location of adhesions after open and laparoscopic procedures is necessary to make specific risk assessments and recommendations for anti-adhesive strategies in both operation techniques.

Adhesiolysis increases the risk of major surgical complications in colorectal surgery. All physicians performing colorectal surgery should be aware of these findings and address the higher intraand postoperative complication rate in preoperative counseling of patients, particularly in those who had multiple previous abdominal operations. Less than 10% of surgeons and gynecologists routinely inform their patients of the risk of adhesions and the potential of adhesion prevention.[35] Awareness of the burden of adhesions might increase the use of adhesion barriers in colorectal and general surgery. Efficacy and safety of barriers has recently been shown in a comprehensive systematic review [36]; adhesion barriers decrease incidence and severity of adhesions as well as operative time at repeat surgery.[37] Small bowel obstruction and female infertility have historically been the focus of adhesion (prevention) research. Future research should include the need for adhesiolysis and adhesiolysis-related complications during repeat abdominal surgery as endpoints. Furthermore, the incidence of postoperative complications and oncological outcome including time to start of adjuvant chemotherapy should be incorporated when including abdominal surgery for malignancies.

Conclusion

Adhesiolysis increases the incidence of iatrogenic bowel injuries and MSRC, prolongs hospital stay and is associated with a higher readmission rate following colorectal surgery.

Disclosure Statement

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4

Prior Abdominal Surgery Jeopardizes Quality of Resection in Colorectal Cancer

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Abstract

Background

Prior abdominal surgery increases complexity of abdominal operations. Effort to prevent injury during adhesiolysis might result in less extensive bowel resection in colorectal cancer surgery. The aim of this study was to evaluate the effect of prior abdominal surgery on the outcome of colorectal cancer surgery.

Methods

A nationwide prospective database of patients with primary colorectal cancer resection in The Netherlands between 2010 and 2012 was reviewed for histopathology, morbidity and mortality in patients with compared to patients without prior abdominal surgery.

Results

9,042 patients with and 17,679 without prior abdominal surgery were analyzed. After prior abdominal surgery 20.7% had less than 10 lymph nodes in the histopathological specimen compared to 17.8% without prior abdominal surgery (adjusted OR 1.17, 95% CI 1.09 -1.26). Adjusted ORs for less than 10 and 12 lymph nodes were significant in colon cancer resection and not in rectal cancer resection. Subgroups of patients who had previous hepatobiliary surgery or other abdominal surgery had a higher incidence of inadequate number of harvested lymph nodes. Prior colorectal surgery increased the percentage of positive circumferential rectal resection margin by 64% (12.5% and 7.6%; adjusted OR 1.70, 95% CI 1.21 – 2.39). For colon cancer morbidity was significantly higher in patients with prior surgery (33.2% and 29.7%; adjusted OR 1.18, 95% CI 1.10 – 1.26), 30-day mortality was comparable (4.7% prior surgery and 3.8% without prior surgery; adjusted OR 1.01, 95% CI 0.88-1.17).

Conclusions

Prior abdominal surgery compromises the quality of resection and increases postoperative morbidity in patients with primary colorectal cancer.

Introduction

Prior abdominal surgery increases the complexity and morbidity of abdominal operations, mainly due to the frequent presence of postoperative intra-abdominal adhesions.[1] The incidence of postoperative intra-abdominal adhesions after previous surgery ranges between 67% and 95%.[2-5] Adhesions may necessitate adhesiolysis, which is time consuming and results in full-thickness or seromuscular bowel injury in one third of the patients.[6] Adhesiolysis and associated bowel injury increase morbidity and mortality.[6, 7] The cautious approach to the bowel during adhesiolysis to avoid injury, might compromise access to the operative field and extent of bowel resection, with possibly smaller or even incomplete resection margins. When access to the pelvic area for performing rectal resection is difficult due to a previous operation, care is taken not to injure ureters or main vessels and nerves, possibly limiting mesorectal excision. A small resection margin, has been identified as a risk factor for poor lymph node harvest.[8] Minimal information is available regarding the effect of previous surgery on quality of resection margin or number of lymph nodes. Two retrospective studies showed no difference in number of harvested lymph nodes and resection margin.[9, 10] Both studies comprised low numbers of patients (n=86 and n=267), and both reported overall mean number of harvested lymph nodes less than 10. This low number possibly reflects inadequate surgical resection or inadequate quality of histopathological examination of the specimen.

Since 2009 the Dutch Surgical Colorectal Audit (DSCA) database is in use to assess and benchmark outcomes of colorectal cancer treatments between hospitals. Prior surgery is one of the many variables recorded in this database. This gave us the opportunity to evaluate the effect of prior abdominal surgery on the outcome of colorectal cancer surgery in more than 25 000 Dutch patients with respect to histopathological quality of resection and postoperative morbidity and mortality.

Patients and Methods

DSCA

Data were retrieved from the Dutch Surgical Colorectal Audit (DSCA), which was initiated by the Dutch Surgical Society to monitor and improve the quality of surgical care in colorectal cancer patients on a national level. The DSCA contains data on primary colorectal cancer resections registered by all 92 Dutch hospitals performing colorectal cancer surgery as from 2009.[11] Recurrent colorectal cancer patients are not included in the database. The data set shows a high level of completeness on most items and a case ascertainment of approximately 95% when compared with the Netherlands Cancer Registry.[12] Details of the dataset regarding data collection and methodology have been published elsewhere.[11] Medical ethics committee approval was not required for this study as all patient and hospital information in the DSCA was anonymous.

In-and exclusion criteria

All patients aged 18 years and older who underwent colonic and rectal cancer resection in the Netherlands between January 2010 and December 2012 were included in this study. Patients who underwent a transanal procedure were excluded from analysis.

Outcomes

Primary outcome measures were number of harvested lymph nodes, circumferential rectal resection margin (CRM), CRM positivity, and completeness of resection in colon cancer. The CRM was considered positive if tumor cells were within 1 mm of the resection margin. Completeness of resection was defined as complete resection (resection with margins free of disease at histopathology, R0) or incomplete resection (margins positive for disease at histopathology, R1 or R2). R1 and R2 were taken together because of relatively small patient numbers with incomplete resection. Besides absolute number of harvested lymph nodes we used cut-offs of 10 and 12 lymph nodes. These are the cut-offs of the Dutch and US guidelines.[13, 14] Secondary outcome measures were postoperative complications and 30-day mortality.

Potential risk factors for adverse oncological or clinical outcome, including patient factors (age, sex, body mass index (BMI), ASA fitness grade, previous abdominal surgery), tumor factors (stage, location, preoperative tumor complications) and treatment factors (neoadjuvant therapy, type of surgical resection, operation technique, urgency of surgery, extent of resection), were extracted from the database. There is no information regarding adhesions in the database (e.g. incidence or severity of adhesions or adhesiolysis time).

Statistical analysis

Univariable analyses were carried out to examine the association previous abdominal surgery and number of harvested lymph nodes, CRM, CRM positivity, completeness of resection, postoperative complications and 30-day mortality. Multivariable logistic regression analyses were performed to correct for possible confounders. A manual stepwise model was used, with inclusion of variables with $P < 0{\cdot}20$. Clinically relevant variables, i.e. neoadjuvant therapy, were added to the statistical model. Conversion from laparoscopic to open technique and tumor localization were not included in the multivariate analysis because of the collinearity between prior operations and conversion, and between localization of the primary tumor and type of resection. Type of resection is highly influenced by the localization of the primary tumor, but the type of resection has a larger influence on clinical and histopathological outcome, especially in case of synchronous tumors.

Subgroup analysis regarding number of lymph nodes and percentage of resections with less than 10 and 12 lymph nodes was performed for colon and rectal cancer separately. Number of lymph nodes

after colon and rectal cancer resection, percentage of colon and rectal cancer resections with less than 10 and 12 lymph nodes, incomplete colon cancer resection and CRM and CRM positivity were analyzed in subgroups of different types of abdominal surgery in history as defined in the database: colorectal surgery (including appendectomy), urogenital surgery, hepatobiliary surgery (including cholecystectomy), upper gastrointestinal surgery (including pancreatic surgery), or other abdominal surgery not otherwise specified. These subgroups of previous surgery were analyzed because reported incidences of adhesion-related and adhesiolysis-related complications differ between different anatomical locations of prior surgery.[2, 15] This subgroup analysis was performed in the cohort 2011-2012, because of a high level of missing data on location of prior surgery in patients operated in 2010. Subgroup analysis by magnitude of the previous operation was not possible because this item is not registered in the database.

Results are reported as odds ratios with 95% confidence intervals. All data were analyzed using SPSS for Windows version 20.0 software (SPSS, Chicago, IL). We excluded per analysis those cases with missing data.

Results

27,341 Colorectal cancer patients were included in the database from 2010 to 2012. After excluding patients younger than 18 years (n=17), transanal procedures (n=344), and patients with missing data of prior abdominal surgery (n=259), 26,721 patients were eligible for inclusion. 9,042 Patients (33.8%) had undergone one or more previous abdominal operations,17,679 patients (66.2%) had no prior abdominal surgery.

Baseline characteristics

Baseline characteristics for the groups with and without prior abdominal surgery are presented in Table 1. All data significantly differed between groups due to large patient numbers. Clinically relevant differences were found for age and sex. Mean age was 71.3 in the prior abdominal surgery group compared to 68.4 in the no prior abdominal surgery group. The prior abdominal surgery group comprised 41.9% male patients compared to 61.3% in the no prior abdominal surgery group.

Histopathological and clinical outcome

Mean number of lymph nodes in the histopathology specimen was 15.2 in the group with and 15.6 in the group without prior abdominal surgery (Table 2). Number of lymph nodes was less than 10 and 12 in 20.7% and 35.8% of patients with prior abdominal surgery compared to 17.8% and 32.8% in patients without prior abdominal surgery. For colonic resection the percentage of patients with less than 10 and 12 lymph nodes was higher in the prior surgery compared to the no prior surgery group.

Table 1: Baseline characteristics Cohort 2010-2012

Prior Abdominal Operations	Yes (N=9,042)	No (N=17,679)	P value
Age	71.3 (±10.8)	68.4 (±11.3)	<0.001
Sex %	41.9% male	61.3% male	<0.001
ASA %			
I	15.5	23.0	<0.001
II	58.2	55.1	
III	24.8	20.0	
IV	1.5	1.8	
V	0.1	0.1	
Urgency operation %			
Elective	85.9	83.8	
Elective after stent placement	0.7	0.6	<0.001
Urgent	7.4	8.0	
Emergency	5.9	7.5	
Unknown	0.2	0.1	
Tumor localization %			
Caecum	15.9	13.3	<0.001
Appendix	0.8	0.4	
Ascending colon	14.6	12.4	
Hepatic flexure	4.8	4.4	
Transverse colon	6.6	5.0	
Splenic flexure	2.3	2.4	
Descending colon	4.7	4.3	
Sigmoid colon	25.3	28.8	
Rectum	24.9	29.0	
Neoadjuvant Therapy % (rectal cancer, N=6457)	N=1921	N=4536	
No	3.4	2.7	0.26
Short course	55.2	54.1	
Long course	5.9	5.8	
Chemoradiation	35.5	37.4	
Operation Technique %			
Open	60.6	54.2	<0.001
Laparoscopic	39. 4	45.8	
Conversion in laparoscopy (n=8589) %			
No	76.5	82.6	<0.001
Early (<30 minutes)	12.5	8.5	
Late (>30 minutes)	11.1	9.0	
Reason for conversion % (N=1406)			
Advanced tumor	14.3	26.9	<0.001
Accessibility	79.1	65.4	
Peroperative complication	6.7	7.7	
Type of Resection %			
Ileocaecal resection/appendicectomy	1.1	0.9	<0.001
Right hemicolectomy	36.1	30.7	
Transverse colectomy	2.7	1.9	
Left hemicolectomy	7.8	7.7	
(Low)Anterior Resection/sigmoidectomy	40.6	47.3	
Subtotal colectomy	1.7	1.4	
Abdominoperineal Resection	7.6	8.5	
Proctocolectomy	0.8	0.6	
Other	1.4	1.0	

Table 1 (continued)**:** Baseline characteristics Cohort 2010-2012

Prior Abdominal Operations	Yes (N=9,042)	No (N=17,679)	P value
T-stage (pathol) %			
1	7.1	6.1	0.001
2	20.8	19.6	
3	55.7	57.6	
4	13.0	13.5	
X	2.1	1.8	
0	1.3	1.4	
N-stage (pathol) %			
0	60.3	57.5	
1	24.3	25.4	<0.001
2	13.8	16.1	
X	1.6	1.0	

Table 2: Histopathological and clinical outcome, cohort 2010-2012

	Prior abdominal operations N = 8949 [b]	No prior abdominal operations N = 17534 [b]	Crude OR/ mean difference (95% CI)	Adjusted OR / mean difference (95% CI) [a]
Number of lymph nodes	15.2	15.6	0.39 (0.11 – 0.66) *	0.37 (0.14 to 0.60) *
- colon cancer	16.1	16.6	0.55 (0.20 – 0.90) *	0.43 (0.15 – 0.71) *
- rectal cancer	12.5	13.0	0.46 (0.11 – 0.81) *	0.14 (-0.23 to 0.50)
< 10 lymph nodes (% pts)	20.7	17.8	1.20 (1.13 – 1.28) *	1.17 (1.09 – 1.26) *
- colon cancer	16.5	13.4	1.28 (1.18 – 1.39) *	1.22 (1.11 – 1.33) *
- rectal cancer	32.9	28.7	1.22 (1.10 – 1.36) *	1.09 (0.96 – 1.23)
< 12 lymph nodes (% pts)	35.8	32.8	1.14 (1.08 – 1.20) *	1.10 (1.04 – 1.17) *
- colon cancer	30.7	27.6	1.16 (1.09 – 1.24) *	1.10 (1.02 – 1.18) *
- rectal cancer	50.8	45.6	1.23 (1.11 – 1.36) *	1.11 (0.99 – 1.24)
Incomplete resection colon cancer (% pts)	3.3	3.8	0.87 (0.73 – 1.02)	0.92 (0.77 – 1.11)
Circumferential rectal resection margin (mm)	11.0	11.1	0.111 (-0.56 to 0.77)	0.10 (-0.82 to 1.02)
CRM positivity (% pts)	10.2	9.1	1.14 (0.94 – 1.38)	1.12 (0.90 – 1.40)
Complications (% pts)	34.5	32.1	1.11 (1.05 – 1.17) *	1.14 (1.07 – 1.21) *
- colon cancer	33.2	29.7	1.17 (1.10 – 1.25) *	1.18 (1.10 – 1.26) *
- rectal cancer	38.0	37.9	1.01 (0.91 – 1.11)	1.04 (0.92 -1.17)
30-day mortality (% pts)	4.7	3.8	1.24 (1.09 – 1.40) *	1.01 (0.88 – 1.17)
- colon cancer	5.3	4.3	1.24 (1.08 – 1.42) *	1.01 (0.86 – 1.18)
- rectal cancer	2.7	2.6	1.04 (0.76 – 1.41)	1.02 (0.70 – 1.47)

* $p < 0.05$

[a] adjusted for male sex, age, ASA fitness grade, type of surgical resection, T stage at histopathology, N stage at histopathology, urgency of surgery, operation technique and neoadjuvant chemotherapy

[b] missing data excluded per analysis

For rectal resection differences were not significant after adjustment for other variables (Table 2). No differences were found in completeness of colonic resection, mean circumferential rectal resection margin and CRM positivity.

There was a small but significant increase in percentage of patients with postoperative complications

after prior surgery (34.5% and 32.1%; adjusted OR 1.14 (95% CI 1.07-1.21). For colonic resection the percentage of patients with complications was higher in the prior surgery compared to the no prior surgery group. For rectal resection no differences was found (Table 2). 30-day mortality was 0.9 percent higher in patients with (4.7%) compared to those without prior abdominal surgery (3.8%). This difference was not significant after adjustment for other variables.

Table 3: Histopathological outcome after colon cancer surgery according to type of prior abdominal surgery, cohort 2011-2012

	Prior colorectal operations N= 1832 [b]	No prior abdominal operations N= 10404 [b]	Crude OR / mean difference (95% CI)	Adjusted OR /mean difference (95% CI) [a]
Number of lymph nodes	16.3	17.1	0.80 (0.33 – 1.27) *	0.61 (0.14 – 1.08) *
< 10 lymph nodes (% pts)	14.2	11.9	1.23 (1.06 – 1.42) *	1.11 (0.94 – 1.30)
< 12 lymph nodes (% pts)	28.9	25.5	1.19 (1.06 – 1.33) *	1.12 (1.00 – 1.27)**
Incomplete resection (% pts)	6.2	3.8	1.66 (1.14 – 2.42) *	1.30 (0.90 – 1.89)
	Prior urogenital operations N= 1790 [b]	No prior abdominal operations N= 10440 [b]	Crude OR / mean difference (95% CI)	Adjusted OR /mean difference (95% CI) [a]
Number of lymph nodes	16.8	17.0	0.23 (-0.24 to 0.71)	0.25 (-0.25 to 0.74)
< 10 lymph nodes (% pts)	13.0	12.1	1.08 (0.93 – 1.26)	1.09 (0.92 – 1.29)
< 12 lymph nodes (% pts)	25.9	26.1	0.99 (0.88 – 1.11)	0.97 (0.86 – 1.10)
Incomplete resection (% pts)	3.3	3.6	0.91 (0.68 – 1.20)	1.03 (0.76 – 1.39)
	Prior hepatobiliary operations N= 922 [b]	No prior abdominal operations N= 11317 [b]	Crude OR / mean difference (95% CI)	Adjusted OR /mean difference (95% CI) [a]
Number of lymph nodes	16.2	17.0	0.77 (0.13 – 1.40) *	0.40 (-0.24 to 1.03)
< 10 lymph nodes (% pts)	14.9	12.0	1.28 (1.06 – 1.54) *	1.28 (1.04 – 1.58) *
< 12 lymph nodes (% pts)	28.2	25.9	1.12 (0.97 – 1.30)	1.09 (0.92 – 1.28)
Incomplete resection (% pts)	3.7	3.5	1.04 (0.73 – 1.49)	1.15 (0.78 – 1.71)
	Prior upper gastrointestinal operations N= 200 [b]	No prior abdominal operations N= 10928 [b]	Crude OR / mean difference (95% CI)	Adjusted OR /mean difference (95% CI) [a]
Number of lymph nodes	21.7	17.0	-4.68 (-6.58 to -2.78)	-0.25 (-1.60 to 1.11)
< 10 lymph nodes (% pts)	16.0	12.0	1.40 (0.95 – 2.05)	1.13 (0.74 – 1.73)
< 12 lymph nodes (% pts)	28.0	25.9	1.11 (0.82 – 1.52)	0.91 (0.65 – 1.27)
Incomplete resection (% pts)	3.3	3.6	0.94 (0.44 – 2.00)	1.08 (0.45 – 2.58)
	Prior other abdominal operations N= 815 [b]	No prior abdominal operations N= 11296 [b]	Crude OR / mean difference (95% CI)	Adjusted OR /mean difference (95% CI) [a]
Number of lymph nodes	16.7	17.0	0.28 (-0.39 to 0.95)	0.12 (-0.55 to 0.79)
< 10 lymph nodes (% pts)	15.1	12.0	1.30 (1.06 – 1.59) *	1.28 (1.02 – 1.59) *
< 12 lymph nodes (% pts)	29.2	25.8	1.18 (1.01 – 1.38) *	1.16 (0.98 – 1.37)
Incomplete resection (% pts)	3.7	3.6	1.04 (0.71 - 1.53)	1.06 (0.71 – 1.60)

[a] adjusted for male sex, age, ASA fitness grade, type of surgical resection, T stage at histopathology, N stage at histopathology, urgency of surgery, operation technique and neoadjuvant chemotherapy

[b] missing data excluded per analysis

* P < 0.05

** P = 0.058

Table 4: Histopathological outcome after rectal cancer surgery according to type of prior abdominal surgery, cohort 2011-2012

	Prior colorectal operations N= 588 [b]	No prior abdominal operations N= 3654 [b]	Crude OR / mean difference (95% CI)	Adjusted OR /mean difference (95% CI) [a]
Number of lymph nodes	12.8	13.3	0.42 (-0.19 to 1.03)	0.22 (-0.41 to 0.85)
< 10 lymph nodes (% pts)	30.4	26.2	1.23 (1.02 – 1.49) *	1.11 (0.89 – 1.38)
< 12 lymph nodes (% pts)	47.4	43.9	1.15 (0.97 – 1.37)	1.03 (0.84 – 1.25)
Circumferential margin (mm)	10.0	10.8	0.83 (-0.12 to 1.77)	0.64 (-0.37 to 1.65)
CRM positivity (% pts)	12.5	7.6	1.74 (1.29 – 2.33) *	1.70 (1.21 – 2.39) *
	Prior urogenital operations N= 531 [b]	No prior abdominal operations N= 3711 [b]	Crude OR / mean difference (95% CI)	Adjusted OR /mean difference (95% CI) [a]
Number of lymph nodes	12.7	13.3	0.56 (-0.08 to 1.21)	0.22 (-0.49 to 0.93)
< 10 lymph nodes (% pts)	29.2	26.5	1.14 (0.94 – 1.40)	1.00 (0.78 – 1.28)
< 12 lymph nodes (% pts)	48.2	43.8	1.19 (1.00 – 1.43)	1.13 (0.91 – 1.41)
Circumferential margin (mm)	12.1	10.5	-1.59 (-2.60 to -0.59) *	-1.80 (-2.95 to -0.65) *
CRM positivity (% pts)	5.2	8.7	0.58 (0.37 – 0.90)	0.71 (0.44 – 1.16)
	Prior hepatobiliary operations N= 271 [b]	No prior abdominal operations N= 3965 [b]	Crude OR / mean difference (95% CI)	Adjusted OR /mean difference (95% CI) [a]
Number of lymph nodes	12.5	13.3	0.76 (-0.11 to 1.63)	0.59 (-0.29 to 1.47)
< 10 lymph nodes (% pts)	32.1	26.5	1.31 (1.01 – 1.71) *	1.21 (0.90 – 1.63)
< 12 lymph nodes (% pts)	53.1	43.8	1.45 (1.14 – 1.86) *	1.32 (1.01 – 1.74) *
Circumferential margin (mm)	9.9	10.8	0.83 (-0.47 to 2.14)	0.60 (-0.78 to 1.98)
CRM positivity (% pts)	6.1	8.4	0.71 (0.42 – 1.21)	0.53 (0.28 – 1.01)
	Prior upper gastrointestinal operations N=81 [b]	No prior abdominal operations N= 3785 [b]	Crude OR / mean difference (95% CI)	Adjusted OR /mean difference (95% CI) [a]
Number of lymph nodes	14.2	13.3	-0.91 (-2.46 to 0.65)	-1.13 (-2.70 to 0.44)
< 10 lymph nodes (% pts)	21.0	26.2	0.75 (0.44 – 1.28)	0.63 (0.34 – 1.18)
< 12 lymph nodes (%)	35.8	43.8	0.72 (0.45 – 1.13)	0.67 (0.40 – 1.12)
Circumferential margin (mm)	12.2	10.9	-1.36 (-3.88 to 1.15)	-1.55 (-4.21 to 1.11)
CRM positivity (% pts)	10.6	7.7	1.43 (0.64 – 3.15)	1.62 (0.70 – 3.77)
	Prior other abdominal operations N= 316 [b]	No priorabdominal operations N= 3885 [b]	Crude OR / mean difference (95% CI)	Adjusted OR /mean difference (95% CI) [a]
Number of lymph nodes	13.0	13.2	0.25 (-0.56 to 1.06)	0.28 (-0.57 to 1.13)
< 10 lymph nodes (% pts)	27.5	26.7	1.04 (0.81 – 1.35)	1.09 (0.81 – 1.48)
< 12 lymph nodes (% pts)	44.9	44.2	1.03 (0.82 – 1.30)	0.98 (0.75 – 1.28)
Circumferential margin (mm)	11.3	10.7	-0.68 (-1.93 to 0.57)	-0.68 (-2.06 to 0.69)
CRM positivity (%)	9.4	8.2	1.73 (1.29 – 2.31) *	1.44 (0.89 – 2.36)

[a] adjusted for male sex, age, ASA fitness grade, type of surgical resection, T stage at histopathology, N stage at histopathology, urgency of surgery, operation technique and neoadjuvant chemotherapy

[b] missing data excluded per analysis

* P < 0.05

Histopathological outcome by type of prior operation

Histopathological results divided by type of prior abdominal surgery, i.e. colorectal surgery, urogenital surgery, hepatobiliary surgery, upper gastrointestinal surgery and other abdominal operations are shown in Table 3 and 4 for colonic and rectal resection, respectively. Prior upper gastrointestinal and urogenital operations did not compromise the quality of oncological resection as reflected by number of lymph nodes, resection margins and completeness of resection, for both colonic and rectal resections. Prior colorectal resection significantly decreased the number of lymph nodes in colon specimens. There was a trend towards a higher percentage of patients with less than 12 lymph nodes in the specimen (28.9% *vs* 25.5%, P = 0.058). An almost two-third increase in patients with CRM positivity of rectal specimens was found (12.5% prior colorectal resection and 7.6 no prior colorectal resection). Prior hepatobiliary surgery and prior other abdominal surgery were associated with increased percentages of patients with less than 10 lymph nodes by 24 and 26, respectively, for colonic resection. For rectal resection, prior hepatobiliary surgery increased the percentage of patients with less than 12 lymph nodes by 21. No significant effects of other abdominal surgery were found for rectal resections.

Discussion

Prior abdominal surgery jeopardizes subsequent abdominal surgical procedures. In the large Dutch Surgical Colorectal Cancer Audit (DSCA) prospective database of colorectal cancer patients increased postoperative complications were demonstrated after prior abdominal surgery. More importantly, prior abdominal surgery had negative effects on histopathological outcome parameters. A higher risk of inadequate numbers of harvested lymph nodes was demonstrated for colonic resections. Prior colorectal surgery was associated with an almost two-third increase of positive circumferential resection margins in rectal cancer patients.

Results of the present study are in agreement with an earlier report of a higher morbidity rate after repeat surgery.[6] In a case-matched study of laparoscopic intestinal resection even a doubling of the incidence of postoperative complications was found after previous midline laparotomy.[1] The DSCA database does not contain information on the extent of prior operations, but only a gross differentiation of anatomical locations where patients had their previous abdominal surgery. It is likely that the prior abdominal surgery group partly consists of laparoscopic or minor surgical procedures such as appendectomy and cholecystectomy, which may account for the relatively small effect on postoperative morbidity found in the present study.

Two small retrospective series demonstrated no impact of prior abdominal surgery on histopathological outcome parameters in colorectal cancer. The number of lymph nodes in colon specimens resected via minilaparotomy was similar between 76 patients with prior abdominal

surgery and 187 patients without prior surgery.[10] Comparison of lymph node numbers and resection margins after laparoscopic colorectal resection in 16 patients with and 44 patients without previous abdominal surgery also revealed no differences.[9] These different results can be explained by the small number of patients included in both studies. The low mean number of lymph nodes, in both studies less than 10, raises doubts about the quality of surgery or histopathological examination.

Multiple studies have been published evaluating risk factors for circumferential margin positivity in rectal cancer surgery. Well recognized risk factors for increased CRM positivity are higher T and N stage, male sex and absence of preoperative chemoradiation.[16-19] Prior abdominal surgery has never been taken into account in previous studies. Since the mesorectal fascia is a retroperitoneal plane, CRM will not be directly affected by intraperitoneal adhesions. However, when the lower abdomen has been explored before surgeons can experience difficulty gaining access to the pelvis. The association of prior colorectal surgery with increase in positive CRM is therefore most likely explained by more challenging surgery and compromised access to the pelvic area due to intraperitoneal adhesions.

The major strength of this study is the use of a very large prospective, complete and validated dataset. However, there are limitations, because the database does not contain descriptions of the presence or severity of adhesions, nor whether adhesiolysis was performed during surgery. Adhesiolysis has demonstrated to increase morbidity and mortality in previous studies [6, 7] and adhesions as a factor for a lower quality of colorectal resection specimens is suggested given the significant findings for prior surgery. The effect of postoperative adhesions on histopathological outcome might even have been underestimated, because a small portion of patients with prior abdominal surgery do not have adhesions.[2-5] On the other hand, intra-abdominal adhesions also occur in patients without prior abdominal surgery. However, the incidence of these adhesions is less than 30% [5] and they are mostly low-grade, easy to separate and do not require a lengthy adhesiolysis.[6]

Some known risk factors for adverse histopathological outcome, such as distance to the nearest bowel resection plane and failure to use a pathology template were not available in the DSCA database.[8] The pathology template for colorectal cancer was introduced in the Netherlands in 2009 and is generally used.

Prior abdominal surgery was not specified in the database except for the 'anatomical location'. Particularly, magnitude (i.e. laparoscopic or minimal invasive approach) of the previous operations and intra-abdominal complications, e.g. postoperative peritonitis could not be assessed. Differences in results between open and minimal invasive prior surgery is expected as there is increasing evidence for a lower risk of adhesion-related complications after laparoscopic surgery.[20] Postoperative peritonitis may render a minimal invasive operation into a very adhesiogenic surgical

procedure. In our own series of consecutive elective colorectal operations 15% of patients who needed adhesiolysis had suffered from previous intra-abdominal infection.[6] The lack of specific information on prior surgery does not make the negative effect of prior abdominal surgery on outcome of colorectal cancer surgery less plausible. At most, we can assume that the negative impact is greater when prior abdominal operations are major. Eight-two percent of patients with prior urogenital operations were women and diagnostic laparoscopy and laparoscopic tubal ligation were probably the most common procedures. Female gender and a minimally adhesiogenic procedure in history may explain the association of prior urogenital procedures with a larger circumferential margin in rectal resection.

Long-term oncological outcome, overall and disease-free survival, are not available in the DSCA database. However, previous studies have shown that an inadequate number of lymph nodes evaluated is associated with an impaired outcome [21, 22], and CRM positivity increases local recurrence risk.[23] Additionally, the higher incidence of postoperative complications might worsen long-term oncological outcome.[24]

With higher life-expectancy and advances in surgical technique the incidence of repeat abdominal surgery has increased. Since adhesion formation is a possible reason for our findings, routine use of anti-adhesive barriers particularly in initial colorectal and hepatobiliary surgery could potentially benefit outcome of reoperations in the same anatomical areas. In a recent systematic review we showed that hyaluronate carboxymethylcellulose has the potential to alleviate the incidence of adhesion related complications in colorectal surgery.[25] Also in two-stage liver surgery hyaluronate carboxymethylcellulose was shown to reduce operation time.[26] The potentially beneficial effect of anti-adhesives on histopathological results of oncological resections should be taken into account in future studies on adhesion prevention.

This present study addresses the negative effect of prior abdominal surgery on the outcome of colorectal cancer surgery. Surgeons should be aware of this effect when performing an oncological resection in patients with abdominal surgery in history to dissect the right planes and obtain sufficient amounts of lymph nodes not compromising the extent of resection. The completeness and quality of preoperative patient informed consent may benefit from the results of this study.

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Multicenter Observational Study of Adhesion Formation after Open- and Laparoscopic Surgery for Colorectal Cancer

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Abstract

Background

After colorectal surgery, most patients develop adhesions, with a high burden of associated complications. Laparoscopy seems to reduce adhesion formation, but evidence to prove this is poor. Trials comparing open- and laparoscopic colorectal surgery have never assessed adhesion formation. Adhesion formation after laparoscopic and open colorectal cancer resection was compared in a prospective observational study of patients, who received liver surgery for colorectal metastases.

Methods

In six liver centers in The Netherlands, data on intra-abdominal adhesions were gathered during liver surgery. Incidence of adhesions to the ventral abdominal wall adjacent to the original incision was compared between patients with prior laparoscopic- and open colorectal resection. Secondary outcomes were incidence of any adhesions, extent and severity of adhesions, and morbidity related to adhesions or adhesiolysis.

Findings

Between March 2013 and December 2015, 151 patients were included. Ninety patients (59·6%) underwent open colorectal resection and 61 patients (40·4%) received laparoscopic colorectal resection. The incidence of adhesions to the previous incision was 78·9% after open colorectal resection compared to 37·7% after laparoscopic colorectal resection ($p<0·001$). The incidence of abdominal wall adhesions and of any adhesion was significantly higher after open resection; the incidence of visceral adhesions did not significantly differ. The extent of abdominal wall and visceral adhesions was significantly higher after open- compared to laparoscopic resection. The median highest Zühlke score at the original incision was significantly higher after open resection. There were no differences in incidence of small bowel obstruction during the interval between the colorectal and liver operations, the incidence of serious adverse events and length of stay after liver surgery.

Interpretation

Laparoscopic colorectal cancer resection is associated with a lower incidence, extent and severity of adhesions to parietal surfaces. Laparoscopy does not reduce the incidence of visceral adhesions.

Funding

No funding.

Research in Context

Evidence Before this Study

A search within the PubMed database was carried out for reports on randomized controlled trials and observational studies on incidence of postoperative adhesions after open- and laparoscopic colorectal surgery, published between January 1990 and December 2012. The search string "Tissue adhesions OR Adhesi* AND Colorectal surgery OR Colorectal surgery OR Colectomy OR Proctocolectomy OR Hartmann OR Pouch surgery OR Ileal pouch-anal anastomosis OR Rectal resection OR Colon resection OR Low anterior resection OR Hemicolectomy" was used, limited to human studies. Reference lists of retrieved articles were searched for relevant additional studies.

The search retrieved no randomized controlled trials on incidence of adhesions after open- versus laparoscopic colorectal surgery. Two observational studies on incidence of adhesions after open- versus laparoscopic colorectal surgery were found. One observational study reported the incidence of adhesions after laparoscopic colorectal surgery only. The reported adhesion incidence was lower after laparoscopic surgery (32%) compared to open surgery (77%). However, the numbers of patients in all studies were small, and none of the studies assessed total incidence of any visceral- and abdominal wall adhesions. Assessment of adhesions was limited to abdominal wall plus adnexal adhesions in the laparoscopic study, and abdominal wall in one comparative study and peristomal adhesions in the other. Additional data on the incidence of adhesions after open colorectal surgery from the control arms (no treatment) of five randomized controlled trials on the efficacy of an adhesion barrier, showed a mean adhesion incidence of 95%. In these trials, the anatomical sites evaluated for adhesions also varied, and none of the trials evaluated total incidence of adhesions. The reported adhesion incidence appears to be lower after laparoscopic- compared to open surgery. The 60% to 100% adhesion incidence reported after open colorectal surgery and the 21% to 50% adhesion incidence reported after laparoscopic colorectal surgery are most likely an underestimation of the actual adhesion rate.

Added Value of this Study

This study was designed to assess the incidence of postoperative adhesions after laparoscopic- compared to open colorectal cancer resection. Assessment of adhesions included both abdominal wall and visceral sites. The most important findings of this study are the significantly lower incidence of adhesions to the abdominal wall after laparoscopic colorectal cancer surgery compared to open colorectal cancer surgery, however, there was no reduction of adhesions between viscera, and yet, a 62% total incidence of adhesions.

Implications of all Available Evidence

This study provides the first high-quality data on the incidence of adhesions after laparoscopic- compared to open colorectal cancer surgery, in which the data enhances knowledge and could contribute to daily practice of many doctors. Lower incidence of adhesions reduces the number of patients with a lifetime risk of adhesion-related complications, adding long-term benefit to the already known short-term benefits of laparoscopic colorectal cancer surgery. The findings of this study are of particular importance for future repeat surgery. Lower incidence of abdominal wall adhesions after laparoscopy facilitates entry, and lowers the risk of bowel injury, at repeat abdominal surgery. The findings of this study reject the common assumption that in the laparoscopic era, adhesions would no longer be an issue. This is consistent with a recent meta-analysis that has reported only small advantages of laparoscopy on the incidence of small bowel obstruction after colorectal surgery. The best method for further prevention of postoperative adhesions in the laparoscopic era should be investigated in future studies. The incidence of adhesions must be quantified for the design of these studies and to guide use of adhesion barriers.

Introduction

Most patients develop adhesions after abdominal surgery. Adhesions can remain asymptomatic, or cause serious complications, such as small bowel obstruction (SBO), secondary female infertility and chronic abdomino-pelvic pain.[1] Adhesiolysis at repeat surgery, particularly complicated by inadvertent bowel defects, can lead to increased mortality, postoperative sepsis, intra-abdominal complications, longer hospital stay, more readmissions, and increased costs.[2] The clinical burden of adhesions and socioeconomic costs are huge, involving millions of patients treated by a great variety of doctors.

Laparoscopy could potentially reduce adhesion formation by decreasing injury to serosal and peritoneal surfaces.[3] Patients who undergo laparoscopy have smaller incisions and there is less tissue manipulation and retraction with instruments, gloved hands and swabs. In laparoscopic surgery, blood loss is usually minimal, and desiccation in the closed peritoneal cavity is less than in open surgery.[4] In contrast, pneumoperitoneum in laparoscopic surgery has been associated with increased propensity of adhesion formation throughout the abdomen, due to the dry gas flow and relative ischemic condition by increased abdominal pressure.[5]

The incidence of adhesions is reported to be 67-93% after open abdominal surgery.[6,7] Data on adhesion formation after laparoscopic surgery is scarce. In experimental studies and small clinical series, laparoscopy demonstrated a lower incidence compared to open surgery.[8-11] Two large population-based register studies showed a lower risk for adhesion-related readmissions and small bowel obstruction after laparoscopic- compared to open colorectal surgery.[12,13] A systematic review of nonrandomized studies showed that all types of laparoscopic procedures slightly lowered the incidence of small bowel obstruction.[1] Altogether, it seems that laparoscopy is beneficial regarding adhesion formation and related complications, however, evidence is lacking from prospective comparative studies with adhesion formation as the primary endpoint.

Demonstrating evidence for reduction of adhesions and related early and late complications by laparoscopy is of scientific-, clinical- and societal interest. Colorectal surgery for cancer is common, and has a high likelihood of adhesion formation and associated complications.[15,16] During the last decade, the laparoscopic approach for colorectal cancer resection has been broadly implemented in surgical practice and has become the standard in some countries.[17,18] In multicenter randomized trials, only minor improvements have been demonstrated on length of stay and blood loss without an impact on survival.[19,20] The broad acceptation of laparoscopic colorectal cancer resection hampers the answer to the question of whether laparoscopy reduces adhesions or not, by reducing the likelihood of a trial with adhesion formation as the primary endpoint. Such a trial would also demand a large number of patients and a second surgery to assess adhesions. It is unlikely that a sufficiently large trial will ever be performed.

An alternative study design was conducted that chose liver surgery for colorectal metastases as an opportunity to assess adhesions after laparoscopic- compared to open colorectal cancer resection. An advantage of this study design is that adhesiolysis related complications of the liver operation could also be investigated.

Methods and Materials

Study Design and Patients

This was a multicenter prospective observational study (clinicaltrials.gov registration number: NCT01720966) designed to compare the incidence and impact of adhesions between open- and laparoscopic colorectal resections. All adult patients undergoing liver surgery between March 2013 and December 2015 in six liver centers in the Netherlands were screened for inclusion. Inclusion criteria were colorectal liver metastases that could be resected or treated with radiofrequency ablation (RFA) after prior colorectal cancer surgery. Treatment of liver metastases was performed by laparotomy or laparoscopy. Exclusion criteria were age under 18 years, mental disorder, prior percutaneous drainage for postoperative abscess, and a history of liver, colorectal (including surgical reintervention for anastomotic leakage), ovarian, or abdominal wall surgery, either before resection of the primary tumor or during the interval between resection of the primary tumor and liver resection. The main logistical reasons to exclude eligible patients were participation in concurrent studies or operating surgeon not trained in adhesion assessment.

Relevant patient, surgical and medical data were prospectively recorded. During treatment of liver metastases, detailed information of adhesions was collected by the surgeon. In the participating centers, one or two surgeons were instructed in adhesion assessment, and adhesion assessment in the first cases was supervised by one investigator (MS). Evaluation of adhesions comprised the location, extent and grading according to the Zühlke classification.[21] Peroperative complications were scored by the operating surgeon directly after surgery. Postoperative complications related to adhesions and adhesiolysis were scored by the ward doctors. Case record forms were checked with the medical records and input of data in the database was independently verified by a second investigator. The local institutional review board waived the need for ethical review (registration number: 2012/502). The study was conducted according to the revised version of the Declaration of Helsinki (October 2008, Seoul).

Variables

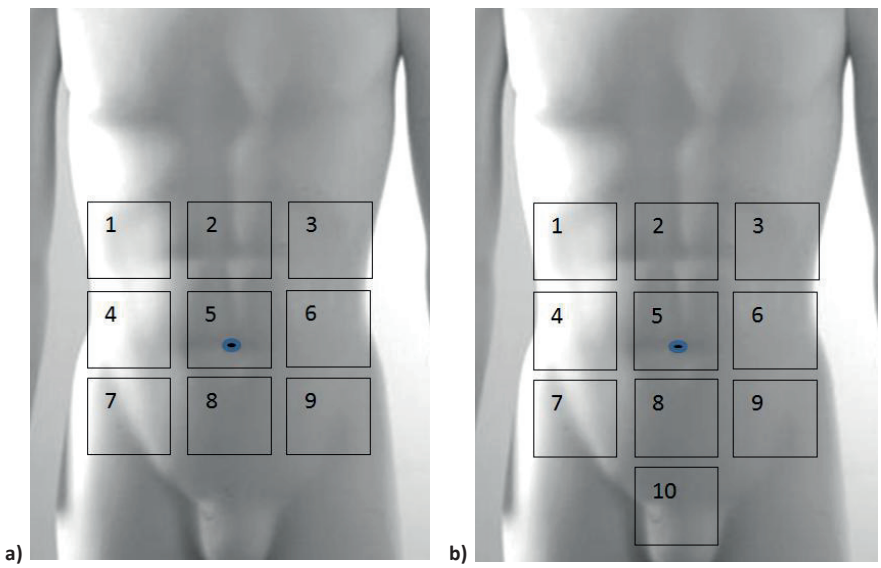
The primary outcome was the incidence of adhesions to the ventral abdominal wall around the incision(s) made for the previous colorectal cancer resection.

Secondary outcomes were: total incidence of adhesions; extent of adhesions; Zühlke classification of

adhesions; performance of adhesiolysis; duration of adhesiolysis; surgical complications; serious adverse events; length of stay in hospital; and episodes of bowel obstruction in the interval between colorectal and liver surgery.

The extent of adhesions to the abdominal wall around the site of the primary incision was determined as estimated percentage of the length of the incision: after laparoscopic colorectal resection, the primary incision was the specimen extraction incision, not the separate trocar incisions. For assessment of the extent of adhesions to the entire ventral abdominal wall, a schematic diagram of the abdominal wall with nine segments was used (figure 1a); extent of adhesions was expressed as the number of segments, in which adhesions were present: visceral adhesions were defined as adhesions between organs, but not to the abdominal wall. As an indication of the extent of visceral adhesions, a schematic diagram was provided, with the addition of a tenth segment for the pelvis (figure 1b). The extent of adhesions was expressed as the number of segments, in which adhesions were present. The severity of adhesions to the ventral abdominal wall around the site of the primary incision and to the ventral abdominal wall was graded according to the Zühlke classification.[21] The gradation is based on the most severe adhesion at the area of the primary incision and to the abdominal wall.

Figure 1: Schematic diagram to assess extent of adhesions as number of segments, in which adhesions are present: **a)** Schematic diagram of the abdominal wall divided into 9 segments. **b)** Schematic diagram of the abdominal cavity divided into 10 segments.



Adhesiolysis time was divided into five categories (1-15 min; 16-30 min; 31-45 min; 46-60 min; >60 min).

Surgical complications included: inadvertent enterotomy; serosal bowel injury; other inadvertent organ injury during adhesiolysis; and delayed diagnosed perforation. Inadvertent enterotomy was defined as any iatrogenic, unintended, full-thickness bowel defect detected during operation. Serosal bowel injury was defined as injury to the serosa, with or without muscular layers of the bowel, without visualization of the bowel lumen or spillage of bowel content. Delayed diagnosed perforation was defined as a bowel defect with spill of gastrointestinal content that was diagnosed postoperatively by imaging at reoperation or at autopsy, and that could not be explained by anastomotic leakage, bowel ischemia, or any other obvious cause of leakage unrelated to adhesiolysis.

Postoperative morbidity noted as serious adverse events included: wound infection (categorized as superficial or deep); intra-abdominal abscess; pneumonia; sepsis; hemorrhage; urinary tract infection; and death. Any episode of bowel obstruction in the interval between colorectal and liver surgery was recorded according to conservative or surgical treatment. Any episode of bowel obstruction within the first two weeks after colorectal resection was considered (prolonged) postoperative ileus.

Baseline demographics included: sex; age; number and type of laparotomies and laparoscopies in history; incision type in previous laparotomies; incision type for specimen retrieval in previous laparoscopies; history of radiotherapy on the abdomen or pelvis; and history of chemotherapy. Operation technique, type of incision, type of liver resection, RFA, and other procedures were recorded during liver surgery. Operation technique was categorized as either open, laparoscopic or conversion to open. Type of liver surgery was categorized as minor or major (≥ three adjacent segments) hepatectomy, RFA without resection or refrain from resection because of unexpected findings. For RFA, the segment(s) within which ablation was performed were registered.

Statistical Methods

The sample size calculation was based on an expected 27% difference in incidence of adhesions to the ventral abdominal wall adjacent to the primary incision, derived from non-published data from a recent observational cohort study [2]. To show this effect with 80% power, and a two-sided α level of 5%, 147 patients were needed.

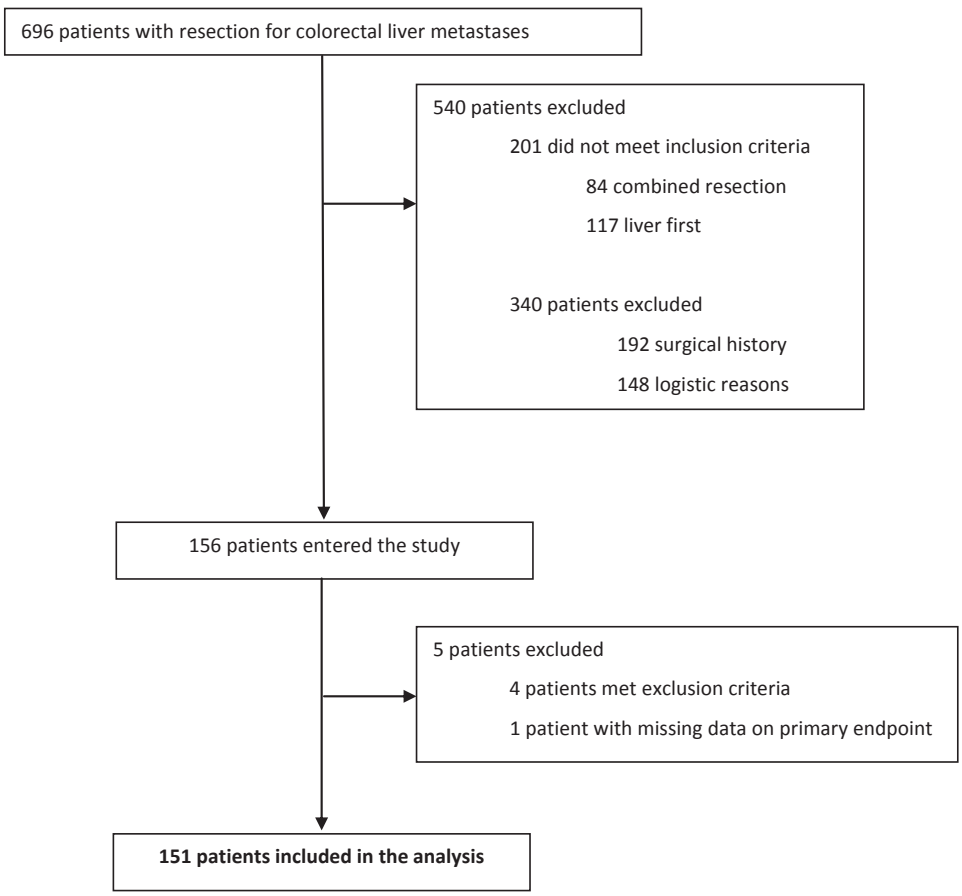
All variables were compared between patients with an open- or laparoscopic colorectal resection. Continuous data were assessed for normality of distribution. In case of normally distributed data, univariate comparisons were performed using independent T-Test and linear regression. With abnormal distribution, continuous data were compared with the Mann-Whitney U Test. For

dichotomous data, Pearson's Chi-Square Test and Logistic Regression testing were performed. Correlations of dichotomous variables with a count less than five per cell were assessed using Fisher's Exact Test. All tests were performed as two-sided. Continuous data are expressed as mean with standard deviation in case of normal distribution, or median with interquartile range (IQR), in case of abnormal distribution, and dichotomous data, as number with percentages.

Alongside raw analyses, corrections for the following potential confounders at the primary endpoint were made: type of colorectal resection; time from colorectal resection; historical laparotomies; historical laparoscopies; pelvic radiotherapy; and chemotherapy.

Cases with missing data per analysis were excluded. SPSS® for Windows version 20·0 Software (SPSS®, Chicago, Illinois, USA) was used for statistical analysis. P<0·05 was considered significant.

Figure 2: Inclusion flow chart



Results

Patients and Baseline Comparisons

Between March, 2013, and December, 2015, 696 patients who underwent a resection for colorectal liver metastases were assessed for eligibility, 540 patients were excluded and 156 patients entered the study (figure 2). After data verification, another five patients were excluded; four patients, because they met predefined exclusion criteria, and one patient, because data on presence of adhesions was missing.

A total of 151 patients were analyzed: 90 patients (59·6%) underwent previous open colorectal cancer surgery and 61 patients (40·4%) laparoscopic colorectal cancer surgery. Baseline characteristics and details of liver surgery are given in Table 1. Median time interval between colorectal resection and liver surgery was 12·5 (IQR 6-25·5) months after open- compared to six (IQR 2-14) months after laparoscopic colorectal resection ($p<0·001$). There were no other significant differences in baseline characteristics. There were no significant differences in technique or type of liver surgery between the groups.

Adhesions

The incidence of adhesions to the ventral abdominal wall around the site of the primary incision was significantly higher after open- compared to laparoscopic colorectal resection (table 2).

The incidence of adhesions to the entire ventral abdominal wall and of any adhesions (adhesions to the abdominal wall and/or visceral adhesions) were also significantly higher after open- compared to laparoscopic colorectal resection. The incidence of visceral adhesions was not significantly different after open- compared to laparoscopic resection. The median percentage of the scar covered with adhesions was not significantly different, 70 (IQR 25-90) and 40 (IQR 10-92·5) after open- and laparoscopic surgery, respectively ($p=0·10$). The extent of adhesions was significantly higher after open- compared to laparoscopic colorectal surgery for both abdominal wall and visceral adhesions (Table 2). The mean highest Zühlke score of adhesions at the site of the primary incision was 2·7 ± 0·70 after open- and 1·8 ± 0·66 after laparoscopic colorectal resection ($p<0·001$). The mean highest Zühlke score of adhesions to the ventral abdominal wall was 2·7 ± 1·1 after open- and 2·0 ± 1·2 after laparoscopic colorectal resection ($p=0·077$).

Small Bowel Obstruction, Adhesiolysis and Complications

The incidence of small bowel obstruction in the time between colorectal resection and liver surgery was four (4·4%) in the open group compared to zero in the laparoscopic group ($p=0·15$). Small bowel obstruction occurred after one, six and 16 months, with time missing in one case.

Table 1: Baseline Characteristics and Details of Liver Surgery.

	Open (n= 90)	Laparoscopic (n=61)	P
Sex			
Male	61 (67·8)	37 (60·7)	0·37
Female	29 (32·2)	24 (39·3)	
Age*	68 (59-73)	65 (59-72·5)	0·36
Colorectal resection (n=150)	(n=90)	(n=60)	
Right colectomy	21 (23·3)	15 (25·0)	0·44
Left colectomy	44 (48·9)	23 (38·3)	
Rectal resection	22 (24·4)	21 (35·0)	
Subtotal colectomy	3 (3·3)	1 (1·7)	
(Extraction) Incision colorectal resection	(n=90)	(n=57)	
Midline	88 (97·8)	22 (38·6)	
Transverse	2 (2·2)	5 (8·8)	
Right iliac fossa	0	9 (15·8)	
Pfannenstiehl	0	19 (33·3)	
Perineal	0	2 (3·5)	
Median time from colorectal resection (months)*	12·5 (6-25·5) (n=90)	6 (2-14) (n=59)	<0·001
Abdominal surgery in history			
0 laparotomy	69 (76·7)	51 (83·6)	0·50
1 laparotomy	17 (18·9)	7 (11·5)	
2 laparotomies	3 (3·3)	3 (4·9)	
3 laparotomies	1 (1·1)	0	
0 laparoscopies	83 (92·2)	57 (93·4)	0·78
1 laparoscopy	7 (7·8)	4 (6·6)	
Pelvic radiotherapy	24 (26·7)	9 (14·8)	0·082
Chemotherapy	47 (52·2)	29 (47·5)	0·57
Liver surgery			
Operation technique			
Open	80 (88·9)	54 (88·5)	0·20
Laparoscopy	10 (11·1)	5 (8·2)	
Laparoscopy converted to open	0	2 (3·3)	
Operation type			
Minor hepatectomy	56 (62·2)	38 (62·3)	0·98
Major hepatectomy	29 (32·2)	19 (31·1)	
Explorative laparotomy	3 (3·3)	2 (3·3)	
RFA without resection	2 (2·2)	2 (3·3)	
RFA	14 (15·6)	16 (26·2)	0·11
RFA 1 segments	7 (50·0)	6 (37·5)	0·73
RFA 2 segments	5 (35·7)	7 (43·8)	
RFA 3 segments	2 (14·3)	2 (12·5)	
RFA 4 segments	0	1 (6·3)	

Data are n (%) or median (IQR); RFA = radiofrequency ablation

Table 2: Primary- and Secondary Endpoints.

	Open (n=90)	Laparoscopic (n=61)	P value
Primary Endpoint			
Adhesions at site of previous incision	71 (78·9)	23 (37·7)	<0·001
Secondary Endpoints			
Adhesions at abdominal wall	73 (81·1)	24 (39·3)	<0·001
Number of segments	3 (2-4)	1 (1-2)	<0·001
Visceral adhesions	53 (58·9)	27 (44·3)	0·077
Number of segments	3 (1-4·5)	2 (1-2)	0·010
Patients with any adhesions	80 (88·9)	38 (62·3)	<0·001
Adhesiolysis	51 (56·7)	21 (34·4)	0·007
Duration of adhesiolysis			
1-15 minutes	42 (82·4)	21 (100)	0·24
16-30 minutes	4 (7·8)	0	
31-45 minutes	1 (2·0)	0	
46-60 minutes	4 (7·8)	0	
>60 minutes	0	0	
Enterotomy	2 (2·2)	0	0·52
Serosal injury	5 (5·6)	0	0·082
Other organ injury	2 (2·2)	0	0·52
Delayed diagnosed perforation	1 (1·1)	0	1·00
Death	1 (1·1)	0	1·00
Wound infection superficial	3 (3·4)	2 (3·3)	1·00
Wound infection deep	2 (2·2)	1 (1·6)	1·00
Intra-abdominal abscess	5 (5·6)	4 (6·6)	1·00
Pneumonia	7 (7·9)	4 (6·6)	1·00
Sepsis	3 (3·4)	0	0·27
Hemorrhage	1 (1·1)	0	1·00
Urinary tract infection	1 (1·1)	4 (6·6)	0·16
Any serious adverse event	15 (16·9)	12 (19·7)	0·66
Length of stay (days)	6·7 (± 4·3)	7·1 (± 4·0)	0·57

Data are n (%), median (IQR), or mean ± SD

Adhesiolysis performed during liver surgery was 1·6 times more frequent in the open colorectal resection patient group (table 2). No adhesiolysis-associated complications occurred during liver surgery in the laparoscopic group, two enterotomies occurred in the open group during 1-15 and 46-60 minutes adhesiolysis. Five patients had serosal injury (adhesiolysis time 1-15 minutes in three patients, 31-45 minutes in one patient

and 46-60 minutes in one patient). Other structures inadvertently injured were the common bile duct in one patient and the gallbladder in one patient (46-60 and 1-15 minutes adhesiolysis time).

There were no significant differences in serious adverse events or length of stay after liver surgery between the laparoscopic and open groups.

Discussion

This study has shown that laparoscopic colorectal cancer surgery is associated with reduced adhesion formation compared to the open procedure, particularly to the ventral abdominal wall. However, more than three in five patients still developed adhesions after laparoscopic colorectal cancer resection.

Knowledge of the incidence of adhesions was mainly derived from old data of open abdominal surgery.[6,7] In the last two decades, a shift towards laparoscopic surgery took place, but open surgery also evolved in this period. Incisions are now generally smaller, which reduces surgical trauma to the abdominal wall and parietal peritoneum. Gloves used in surgical procedures no longer contain powder, and new energy devices cause less peritoneal injury.[4] Despite these developments, the incidence of adhesions after open colorectal resections was almost 90%, and was comparable with old data, versus 62% in laparoscopic resections.

This incidence of adhesions in the laparoscopic group challenges the broad opinion that laparoscopy minimizes adhesion formation. The benefit was mainly regarding adhesions to the abdominal wall and was most likely due to small incisions, no retractors and only instrument manipulation. Laparoscopy did not reduce incidence of adhesions between viscera. The similar tissue dissection and remaining peritoneal wound surfaces in both approaches seem to outweigh the differences in invasiveness. The number of patients without any adhesion (38%) has important clinical consequences, because without further abdominal surgery, their lifetime risk of adhesion-related complications is zero. The decrease in extent and severity of adhesions after laparoscopic colorectal cancer surgery benefit repeated surgery by reducing time and difficulty of adhesiolysis, but might not decrease adhesive small bowel obstruction rate.

Studies of adhesion formation after open versus laparoscopic colorectal surgery are limited to three small comparative series. In two studies, patients underwent a diagnostic laparoscopy during loop ileostomy closure, after prior proctocolectomy or low anterior resection.[10,11] In another study, patients with prior colorectal resection underwent laparoscopy for various reasons.[9] The primary endpoint was a video-assessed adhesion extent and severity score of adhesions to the abdominal wall, which was lower after laparoscopy in all studies. The incidence in the largest series was 30·8 % (four patients out of 13) in the laparoscopic surgery group, compared to 97·0% (32 patients out of 33) in the open surgery group.[9] The main drawback of these studies was the incomplete assessment of adhesions, and in particular, that information on clinically relevant visceral adhesions was lacking. The use of video-laparoscopy to map adhesions at ileostomy takedown is questionable because intra-abdominal view can be hindered by dense adhesions in the proximity of the stoma, and without additional trocars, visceral adhesions are difficult to assess. In the present study, the majority of patients had their adhesions assessed by open surgery with an excellent view of the abdominal

cavity.

The difference between the open and laparoscopic group (median 12·5 versus six months) regarding time interval between liver surgery and colorectal surgery, might be attributed to the recent shift from open towards laparoscopic colorectal surgery in the Netherlands.[17] Recently performed colorectal resections, were more often performed by laparoscopy. Faster recovery of colorectal resection after laparoscopy might also have contributed. Most likely, adhesion rate is not affected by this interval difference, since experimental studies demonstrate that fibrous adhesions form in the first weeks after peritoneal injury, do not disappear, and only can become more filmy in time.[22] The shorter time between laparoscopic colorectal and liver surgery could explain the absence of small bowel obstruction, because a first episode of adhesive small bowel obstruction can occur many years after abdominal surgery.[23] Although a recent meta-analysis demonstrated a lower incidence of small bowel obstruction after laparoscopic compared to open colorectal surgery, the relative difference was small.[24]

The present large prospective study is the first to provide complete information on adhesion formation after laparoscopic colorectal cancer surgery, potentially improving patient counseling, risk assessment in repeated surgery, and selecting adhesion barriers.

A limitation of the present study was the lack of details on initial colorectal surgery. Perforated- or locally advanced colorectal tumors increase adhesion formation, and presumably these tumors were removed by open surgery.[3,4] However, based on national registry data the number of patients with these indications is small.[15]

The high number of excluded patients was a potential threat to the external validity of this study. Many patients at risk for more extensive and severe adhesions after colorectal surgery due to prior other abdominal surgery were excluded. This probably also contributed to the low number of adhesiolysis related surgical complications in the open surgery group.[2]

With the increasing number of reoperations in oncological surgery, the burden of adhesiolysis is expected to rise further. Oncological treatment can be seriously impaired due to diminished accessibility of the abdomen in case of (recurrent) liver metastases, local recurrence, or peritoneal metastases.[25,26] Taking into account the increase of reoperations in future patients with colorectal cancer and the better prevention of de novo adhesions rather than adhesion reformation after adhesiolysis, maximal reduction of adhesions through a combination of minimally invasive surgery and anti-adhesives should be the aim at initial colorectal surgery.[27] Such an approach also decreases operation time, prevents complications and may lead to better oncological outcome and survival.[28-30]

In conclusion, adhesion formation is reduced after laparoscopic- compared to open colorectal cancer surgery. However, the majority of patients still develop adhesions after laparoscopic colorectal cancer resection. Laparoscopy does not seem to have an effect on visceral adhesion formation

incidence. Thus, patients remain at risk for developing small bowel obstruction, and reoperations near the same surgical site can still involve adhesiolysis with associated complications.

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6

Benefits and harms of adhesion barriers for abdominal surgery: a systematic review and meta-analysis

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Abstract

Background

Formation of adhesions after peritoneal surgery results in high morbidity. Barriers to prevent adhesion are seldom applied, despite their ability to reduce the severity of adhesion formation. We evaluated the benefits and harms of four adhesion barriers that have been approved for clinical use.

Methods

In this systematic review and meta-analysis, we searched PubMed, CENTRAL, and Embase for randomised clinical trials assessing use of oxidised regenerated cellulose, hyaluronate carboxy methylcellulose, icodextrin, or polyethylene glycol in abdominal surgery. Two researchers independently identified reports and extracted data. We compared use of a barrier with no barrier for nine predefined outcomes, graded for clinical relevance. The primary
outcome was reoperation for adhesive small bowel obstruction. We assessed systematic error, random error, and design error with the error matrix approach. This study is registered with PROSPERO, number CRD42012003321.

Findings

Our search returned 1840 results, from which 28 trials (5191 patients) were included in our meta-analysis. The risks of systematic and random errors were low. No trials reported data for the effect of oxidised regenerated cellulose or polyethylene glycol on reoperations for adhesive small bowel obstruction. Oxidised regenerated cellulose reduced the incidence of adhesions (relative risk [RR] 0.51, 95% CI 0.31–0.86). Some evidence suggests that hyaluronate carboxymethylcellulose reduces the incidence of reoperations for adhesive small bowel obstruction (RR 0.49, 95% CI 0.28–0.88). For icodextrin, reoperation for adhesive small bowel obstruction did not differ significantly between groups (RR 0.33, 95% CI 0.03–3.11). No barriers were associated with an increase in serious adverse events.

Interpretation

Oxidised regenerated cellulose and hyaluronate carboxymethylcellulose can safely reduce clinically relevant consequences of adhesions.

Introduction

Adhesions are the most common cause of long-term complications from abdominal surgery. They can cause small bowel obstruction, injury at reoperations, female infertility, and chronic pain.[1-5] Adhesions can affect the quality of life of millions of patients, jeopardise life expectancy, and result in more than US$2 billion dollars of health-care costs in the USA yearly.[2,6,7]

Steps are rarely taken to prevent adhesion despite evidence that adhesion barriers reduce their formation.[1,8-11] Underestimating the burden of adhesions seems to be an important explanation for the lack of use of adhesion barriers.[12] Unlike other postsurgery complications, the consequences of adhesion formation include various clinical entities that are often dealt with by specialists other than the surgeon who did the initial operation.[4, 5,7] Additionally, many questions exist about the indications for adhesion barriers, cost-effectiveness, and which barrier to use.[12,13]

Cochrane reviews have not answered the questions of efficacy and safety of barriers.[14-16] More than 20 different membranes and liquids have been investigated in clinical studies for use as adhesion barriers. Many were either unsuccessful in reducing the formation of adhesions or were only assessed using outcomes of little clinical importance.[17,18] Some were even associated with detrimental effects.[19] Results were dispersed over three reviews and only trials in gynaecological or colorectal surgery were included. Thus, appraising the available evidence about the use of adhesion barriers remains difficult.

The error matrix approach has been specifically developed for such situations, in which the possible benefits and harms of an intervention are difficult to summarise.[20] This approach consists of assessment of the three dimensions of systematic error, random error, and design error. The three dimensions of error can be presented in a three dimensional plot so that the relevance and strength of evidence for different benefits and harms can be judged at a single glance.

We assessed the benefits and harms of use of adhesion barriers for all types of abdominal surgery by such an approach.

Methods

Study design and systematic review

We assessed the results of our systematic review and meta-analyses by the error matrix approach. The error matrix approach has been validated in systematic reviews of cholecystectomy and inguinal hernia repair.[21,22] We included randomised trials evaluating the four adhesion barriers that have been approved for clinical use by legislative authorities in Europe and the USA: hyaluronate carboxymethylcellulose (Seprafilm®, Sanofi, Paris, France), oxidised regenerated cellulose (Interceed®, Johnson & Johnson, New Brunswick, NJ, USA), icodextrin 4% solution (Adept®, Baxter, Deerfield, IL, USA), and polyethylene glycol (Spraygel®, Sprayshield®, Confluent Surgical, Waltham,

MA, USA).

We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials with Mesh descriptors including: “carboxymethylcellulose”, “hyaluronic acid”, “icodextrin”, “polyethylene glycols”, “tissue adhesions”, “intestinal obstruction”, “infertility, female”, “abdominal pain”, “pelvic pain”, and “intestinal disease/surgery”. The appendix shows the full search strategy. We did not apply any language restrictions and included all relevant articles up to Feb 2, 2013. Only randomised trials were included. We also searched the reference lists of identified trials, for further references, including those published in grey literature. We did additional searches to find relevant grey literature and unpublished trials (appendix).

RPGtB and MWJS identified eligible reports; discrepancies were resolved through discussion. We applied the following inclusion criteria to the titles and abstracts of the search results: patients undergoing intraperitoneal surgery, application of one of the four adhesion barriers, and report of adhesion-related outcomes. Results of some trials were reported in more than one report. Information from the different reports was linked and analysed as a single trial.

We assessed all trials for the risk of bias (measured by the level of evidence), the risk of random error, and the design error.[20] We present data in a three-dimensional Manhattan plot. We assessed the risk of systematic error with the Cochrane Collaboration's instrument for bias risk assessment.[23] Six components associated with the risk of bias were assessed: generation of the allocation sequence, allocation concealment, masking of outcome assessors, selective outcome reporting, incomplete follow-up, and other potential sources of bias. Trials with a low risk for all six components were defined as having an overall low risk of bias. Trials in which one or more of the six bias components were unclear or had high risk of bias were defined to be at high risk of bias. Because masking the surgeon to allocation is impossible, trials in which patients and outcome assessors were masked were deemed to have a low risk of bias for masking. Additionally, we recorded data about funding sources.

The risk of random error is the risk of drawing a false conclusion based on sparse data. This risk is quantified as the p value. However, because random low (and random high) p values might occur during accumulation of data and sequential testing, they do not sufficiently represent the risk of random error between different studies.[24] The standard error (SE) measures the amount of variability in the sample mean; it indicates how closely the population mean is likely to be estimated by the sample mean. We therefore used SE to evaluate the risk of random error, using the algorithms suggested by the Cochrane collaboration.[23] We defined small risk of random error as an SE of less than 0.20 and moderate risk as an SE of less than 1.00. Studies with higher risk of random error (≥1.00) fell outside the range of the plot.

We assessed design error (external validity) by classifying the clinically relevant outcome measures

according to the Grading of Recommendations Assessment, Development and Evaluation approach.[25] We assessed publication bias with funnel plots. Raw data from unpublished studies and studies using adhesion-related outcomes other than those predefined were reported separately.

We compared use of a barrier with no barrier for nine predefined outcomes. The primary outcome was reoperation for adhesive small bowel obstruction. We also assessed serious adverse events, total incidence of adhesions, reoperation time, small bowel obstruction from any cause, site-specific incidence of adhesions, and adhesion score.

Statistical analysis

We used the Mantel-Haenszel method for dichotomous data, presented as relative risks (RR) with 95% CIs. We used the inverse variance method to pool continuous data; results are presented as standardised mean difference with 95% CIs. We assessed statistical heterogeneity with Cochran's test and I2. In the absence of statistical heterogeneity we used a fixed-effect model, otherwise we used a random-effects model. We did the analyses with Review Manager (version 5.1) and R (version 2.12.0). [26]

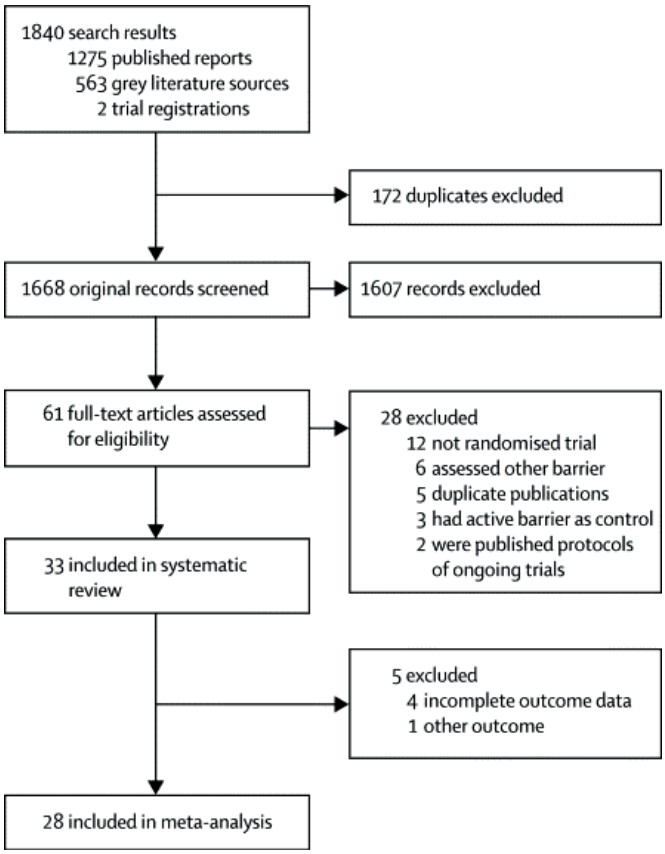
We did three subgroup analyses. First, we compared the pooled results of trials with a low overall risk of bias with the pooled results from trials with a high overall risk of bias. Second, we compared the pooled results of trials with a low risk of funding bias with trials with an unclear or high risk for funding bias (trials sponsored by industry). Third, trials with clinical heterogeneity were not pooled into one overall effect estimate. Clinical heterogeneity was assessed by subgroup according to the type of operation (upper alimentary tract, lower alimentary tract or colorectal, abdominal wall, gynaecological, or urological surgery). All subgroup analyses were tested for interactions.

The full review protocol is registered with PROSPERO (number CRD42012003321) and shown in the appendix.

Role of the funding source

There was no funding source for this study. RPGtB and HvG had full access to all data in the study and had final responsibility for the decision to submit for publication.

Figure 1: Study selection



Results

Our search returned 1840 results, from which we included 33 trials assessing 5381 patients in our systematic review (Fig 1, table 1). Five trials either reported on outcomes not included in the predefined outcomes or had incomplete outcome data. Thus, 28 trials assessing 5191 patients were included in the meta-analyses. 20 trials were of gynaecological surgery, nine of colorectal surgery, and one each of gastric, hepatic, general paediatric, and small bowel obstruction surgery.

Outcome measures were reoperation for adhesive small bowel obstruction (six trials), serious adverse events (14 trials), overall incidence of adhesions (six trials), operation time (three trials),

Table 1: Trials included in systematic review

Trial	design	Area	randomised	Patients	intervention	control	outcome	funding
Oxidized regenerated cellulose								
[Nordic Adhesion Prevention Study Group] (1995)	multicentre (8 hospitals, 2 countries)	Gynaecological	66 pts; unit of randomization: ovaries	Female infertility patients with bilateral tubal disease undergoing complete adhesiolysis	adnex and fallopian tube covert with sheet of oxidized regenerated cellulose	other side was left uncovered	Site specific adhesions; adhesion score	Johnson & Johnson AB, Stockholm, Sweden
Azziz (1993)	multicentre (13 hospitals)	Gynaecological	134 pts; unit of randomization: pelvic sidewall	Female patients undergoing fertility surgery requiring bilateral adhesiolysis	One sheet of oxidized regenerated cellulose was applied to one sidewall after complete adhesiolyis	other sidewall was left uncovered	Site specific adhesions	Partial grant from Johnson & Johnson incorporate.
Franklin (1995)	multicentre (13 hospitals)	Gynaecological	57 pts; unit of randomization: ovaries	Female infertility patients with bilateral tubal disease undergoing complete adhesiolysis	One sheet of oxidized regenerated cellulose was applied to one ovary	other side was left uncovered	Site specific adhesions; adhesion score	Johnson & Johnson Medical inc, Arlington, Texas.
Geldrop (1994)*	Unknown	Gynaecological	20 pts; unit of randomization: ovaries	female patients undergoing bilateral ovarian surgery	One sheet of oxidized regenerated cellulose was applied to one ovary	other side was left uncovered	Adhesion score -abstract only, incomplete data-	Not reported
Greenblatt (1993)	single centre	Gynaecological	8 pts; unit of randomization: ovaries	female patients undergoing fertility surgery for polycystic ovarian disease	One sheet of oxidized regenerated cellulose was applied to one ovary	other side was left uncovered	adhesion score	Medical research council of Canada and Ethicon (a Johnson & Johnson company)
Keckstein (1996)	open-label single centre	Gynaecological	25 pts; unit of randomization: ovaries	Female patients undergoing bilateral ovarian cystectomy	One sheet of oxidized regenerated cellulose was applied to one ovary	other side was left uncovered	Site specific adhesions	Johnson & Johnson medical inc.
Li (1994)	single centre	Gynaecological	28 pts; unit of randomization: pelvic sidewall	Female patients undergoing bilateral pelvic adhesiolysis	One sheet of oxidized regenerated cellulose was applied on to one sidewall after complete adhesiolyis	other sidewall was left uncovered	adhesion score	Johnson & Johnson medical Ltd, provided adhesions barriers and financial support
Mais (1995a)	single centre	Gynaecological	32 pts.	Premenopausal women undergoing laparoscopic endometriosis surgery	Operated area was covered with one to three sheets of oxidized regenerated cellulose	No barrier	Incidence of adhesions	Not reported
Mais (1995b)	single centre	Gynaecological	50 pts.	Premenopausal women undergoing laparoscopic myomectomy	Operated area was covered with three sheets of oxidized regenerated cellulose	No barrier	Incidence of adhesions; adhesion score	Not reported
Saravelos (1996)	single centre	Gynaecological	27 pts; unit of randomization: ovaries	Female patients undergoing laparoscopic fertility surgery for polycystic ovarian disease	One sheet of oxidized regenerated cellulose was applied to one ovary	other sidewall was left uncovered	Site specific adhesions; adhesion score	Johnson & Johnson medical Ltd, provided adhesions barriers and financial support
Sekiba (1992)	multicentre (12 hospitals)	Gynaecological	63 pts; unit of randomization: pelvic sidewall	Female patients undergoing laparotomy for endometriosis	One sheet of oxidized regenerated cellulose was applied to one sidewall after complete adhesiolyis	The other sidewall was left uncovered	Site specific adhesions	Partial grant from Johnson & Johnson
Tinelli (2011)	multicentre	Gynaecological	694 pts	Female patients undergoing open or laparosocpic myomectomy	Operative area covered by sheets of Oxidized regenerated cellulose	No barrier	Incidence of adhesions, serious adverse events	Not reported, No conflicts of interests declared in financial disclosure

Hyaluronate carboxymethylcellulose								
Beck (1997)	multicentre	Colorectal	183 pts	Patients undergoing open colectomy and ileal J-pouch anal anastomosis	Hyaluronate carboxymethylcellulose (on average little more than 2 sheets)	No barrier	Site specific adhesions; adhesion score, serious adverse events	Not reported, one contributing author working for Genzyme corporation
Diamond (1996)	multicentre (19 hospitals)	Gynaecological	127 pts	Female patients undergoing open myomectomy surgery	One up to two sheets of Hyaluronate carboxymethylcellulose	No barrier	Adhesion score	Genzyme corporation
Dupré (2013)	Multicentre (8 hospitals)	Hepatic surgery	54 pts	Patients undergoing two- stage liver resection	Four sheets of Hyaluronate carboxymethylcellulose between liver lobes	No barrier	Adverse events; Reoperation for ASBO; operation time	Ministry of Health, France. Bariers provided by Genzyme
Fazio (2006)	multicentre, multinational single blinded	Colorectal	1791 pts	Open colorectal surgery for benign disease	Hyaluronate carboxymethylcellulose	No barrier	Reoperation for ASBO; SBO (any cause), serious adverse events	Genzyme Corporation
Hayashi (2008)	multicentre (3 hospitals)	Gastric	150 pts	Patients undergoing gastrectomy for malignant disease	Hyaluronate carboxymethylcellulose	No barrier	Reoperation for ASBO; SBO (any cause), serious adverse events	Nihon University
Inoue (2005)	Single centre	General pediatric	122 pts	Various procedures in general surgery in pediatric patients	Hyaluronate carboxymethylcellulose	No barrier	Post hoc analysis of operative time from 17 patients	Not reported
Kusunoki (2005)	multicentre (3 hospitals)	Colorectal	62 pts	Patients undergoing open surgery for rectal malignancy	Hyaluronate carboxymethylcellulose	No barrier	Reoperation for ASBO; SBO (any cause) Site specific adhesions	Not reported
Park (2009)	single centre study	Colorectal	427 pts	Patients undergoing radical resection for rectal or sigmoid cancer	Hyaluronate carboxymethylcellulose	No barrier	Reoperation for ASBO; SBO (any cause), serious adverse events	IN-SUNG foundation for Medical research
Salum (2006)	multicentre (15 hospitals)	Colorectal	191 pts	Patients undergoing colorectal surgery with temporary ileostomy	Hyaluronate carboxymethylcellulose	No barrier	Site specific adhesions; adhesion score, serious adverse events	Genzyme Corporation
Vrijland (2002) / Van der Wal (2011)	multicentre (10 hospitals)	Colorectal	67 pts	Patients undergoing open Hartmann's procedure	Hyaluronate carboxymethylcellulose	No barrier	Site specific adhesions, serious adverse events, Chronic abdominal complaints	Not reported
Icodextrin								
Catena (2011)	single centre	Adhesive bowel obstruction	181 pts	Patients operated for adhesive small bowel obstruction	Icodextrin	No barrier	Reoperation for ASBO; small bowel obstruction(any cause), serious adverse events	Baxter BioSurgery (Italy)
diZerega (2002)	open-label multicentre (5 hospitals)	Gynaecological	62 pts	Female patients undergoing laparoscopy for infertility or chronic pelvic pain	Icodextrin	No barrier	Incidence of adhesions	Not reported

Kossi (2009)	double blinded single centre	Colorectal	23 pts	Patients undergoing Hartmann's procedure	Icodextrin	Ringers lactate solution as placebo	Operation time, serious adverse events	Iinvestigator driven. Limited support from Shire pharmaceuticals/ Baxter BioSurgery
Trew (2011)	double blinded multicentre (25 hospitals)	Gynaecological	498 pts	Female patients undergoing removal of myomas or endometriotic cysts	Icodextrin	Ringers lactate solution as placebo	Adhesion score, serious adverse events	Baxter BioSurgery
PEG adhesion barrier								
Banasiewicz (2011)*	Multicentre	Colorectal	11 pts	Patients undergoing colorectal surgery	PEG adhesion barrier	Not reported	Adhesion score, Operative time - abstract only, data incomplete-	Confluent Surgical inc.
De Wilde (NA)*	Multicentre	Gynaecological	15 pts	Female patients undergoing laparoscopic resection of fibroid or myoma	PEG adhesion barrier	Not reported	Incidence of adhesions - abstract only, data incomplete-	Confluent Surgical inc.
Johns (2003)*	Single centre	Gynaecological	22 pts	Female patients undergoing bilateral adnexal surgery	PEG adhesion barrier	No barrier	Extent of adhesions	Confluent Surgical inc.
Mettler (2008)	multicentre (6 hospitals, 3 countries)	Gynaecological	72 pts	Female patients undergoing open or laparoscopic myomectomy	PEG adhesion barrier	Ringers lactate solution as placebo	Adhesion score, serious adverse events	Angiotech Pharmaceuticals
Mettler (2004)	multicentre (2 hospitals)	Gynaecological	64 pts	Female patients patients undergoing open or laparoscopic myomectomy	PEG adhesion barrier	No barrier	Incidence of adhesions	Not reported
Tjandra (2008)	single centre	Colorectal	40 pts	Patients undergoing low anterior resection or ileal pouch anal anastomosis with temporary loop ileostomy	PEG adhesion barrier	No barrier	adhesion score; operation time, serious adverse events	Confluent Surgical inc.
Ten Broek (2012)	single centre	Gynaecological	15 pts	Female patients undergoing laparoscopic treatment of benign gynaecological disease	PEG adhesion barrier	No barrier	Incidence of adhesions; adhesion score, serious adverse events	Investigator driven. Limited support from Confluent Surgical inc.

ASBO= adhesive small bowel obstruction, SBO= small bowel obstruction. *Not included in meta-analaysis.

small bowel obstruction by any cause (five trials), site-specific incidence of adhesions (ten trials), and adhesion score (13 trials). These outcome measures were ranked according to their clinical relevance for the patient according to Grading of Recommendations Assessment, Development and Evaluation with reoperation for adhesive small bowel obstruction as the highest relevance and adhesion score as the lowest (table 2).

Table 2: Predefined outcomes ranked according to Grading of Recommendations Assessment, Development and Evaluation by relevance according to the patients' perspective

Crucial for decision making	9	Reoperation for adhesive small bowel obstruction
	8	Serious Adverse Events
Important for decision making	6	Total incidence of adhesions
	5	Operation time of reoperation
	4	Small bowel obstruction(any cause)*
Limited importance	2	Site specific incidence of adhesions
	1	Adhesion score

* Includes small bowel obstructions not caused by adhesions

Roughly two-thirds of trials adequately generated an allocation sequence (Fig 2). Most studies had adequate allocation concealment and masking of the outcome assessors. Follow-up methods and description of reasons for loss to follow-up were adequate in the majority of trials. The risk of outcome bias through selective reporting was low for some studies. The primary endpoint was changed during one trial.[53] The timing of second look procedures varied widely in the study by Tinelli and colleagues.[11] One trial was stopped prematurely because of organisational difficulties.[57]

Overall, four trialshad a low risk of bias based on all six domains (figure 2).[1,8,9,55]

Industry sponsored 16 trials (57%) and sponsoring was not reported for seven trials (25%). Two trials assessing hyaluronate carboxymethylcellulose were initiated and sponsored by independent parties.[39,42] Another three trials were investigator driven, but the manufacturer supplied the adhesion barrier.[38,48,57] The results from investigator-driven trials were similar to the results from industry-sponsored trials (appendix).

The risk of random error (SE) was small for adhesion score in eight trials, and overall incidence of small bowel obstruction by any cause in one trial. Funnel plots appeared to be symmetrical: trials did not report extreme values (outside 95% CI) by most analyses (appendix). Three additional trials from grey literature and trial registries had limited available outcome data. Their findings accorded with the results of published studies (appendix).

Oxidised regenerated cellulose is a solid barrier in the form of a knitted fabric. After application on the injured peritoneum it swells and becomes a gel. The gel breaks down to monosaccharides and is metabolised by glycosidases of peritoneal macrophages within 4 days to 2 weeks.[58,59] Oxidised regenerated cellulose was compared with no adhesion barrier in 11 trials (1184 patients).[8,9,11,27-29,31-35] All trials were of gynaecological patients. Two trials had low risk of bias.[8,9] Eight trials were explicitly

industry-sponsored and sponsorship was unclear for three trials. In eight studies (408 patients), each patient served as their own control by having one side of the pelvis randomly assigned to receive an adhesions barrier. The remaining three trials included 776 patients in a parallel group design.

Figure 2: Methodological quality of trials included in meta-analysis.

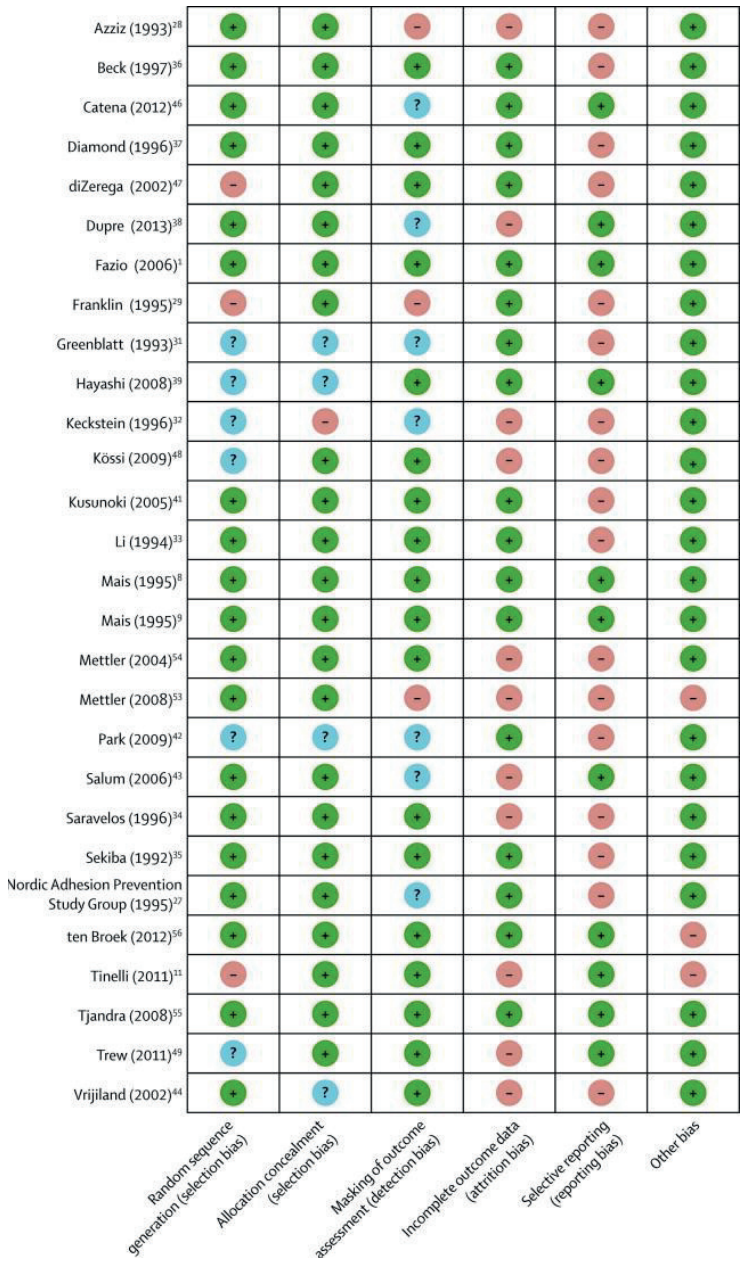


Figure 3 shows the results of our meta-analysis. Figure 4 shows overall results from the included trials of oxidised regenerated cellulose. No trials reported data for the effect of oxidised regenerated cellulose on reoperations for adhesive small bowel obstruction. Evidence shows the beneficial effects of oxidised regenerated cellulose on the incidence of adhesions and adhesion scores from trials with low risks of both systematic and random error. No evidence exists for a beneficial effect on the incidence of serious adverse events (appendix).

No trials reported data for pregnancy rate with oxidised regenerated cellulose. Incidence of serious adverse events after myomectomy was much the same between the two groups in one trial (RR 0.80, 95% CI 0.46–1.39).[11] Postoperative fever was the only serious adverse event recorded in both groups.

Figure 3: Results of key comparisons of four adhesion barriers

Random effect applied for the incidence of adhesions after application of oxidised regenerated cellulose and the incidence of serious adverse events after application of hyaluronate carboxymethylcellulose; fixed effects applied for the incidence of serious adverse events after application of icodextrin and the incidence of adhesions after application of polyethylene glycol. Only subtotals were pooled for hyaluronate carboxymethylcellulose and icodextrin because of heterogeneity in types of operations. The appendix shows forest plots for other comparisons.

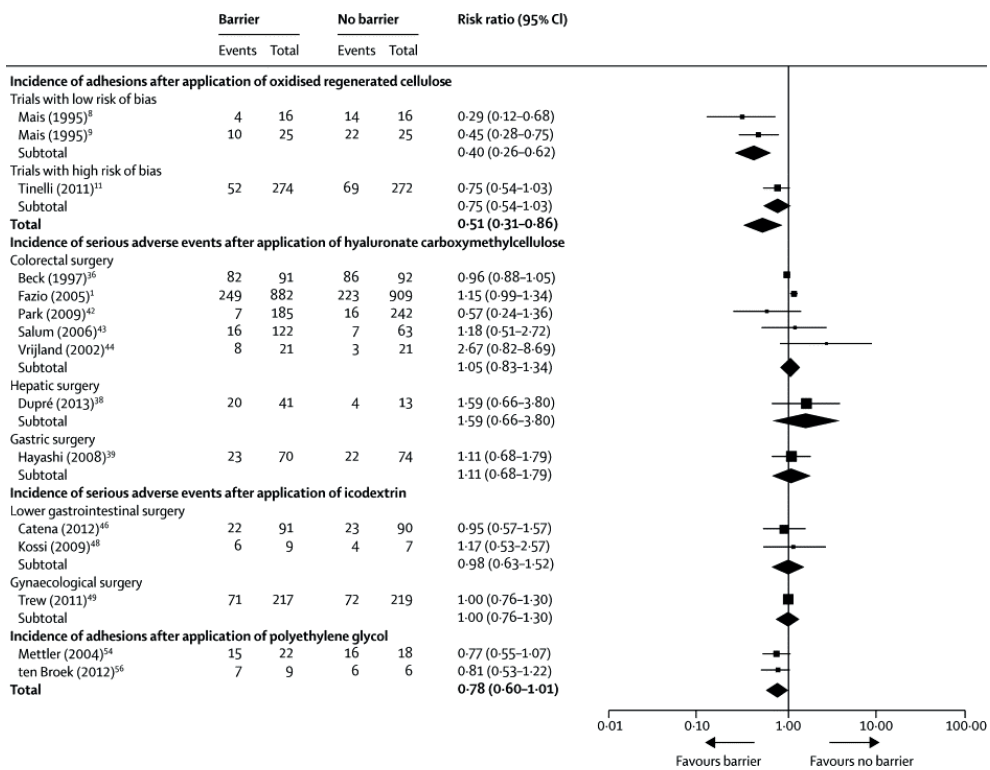
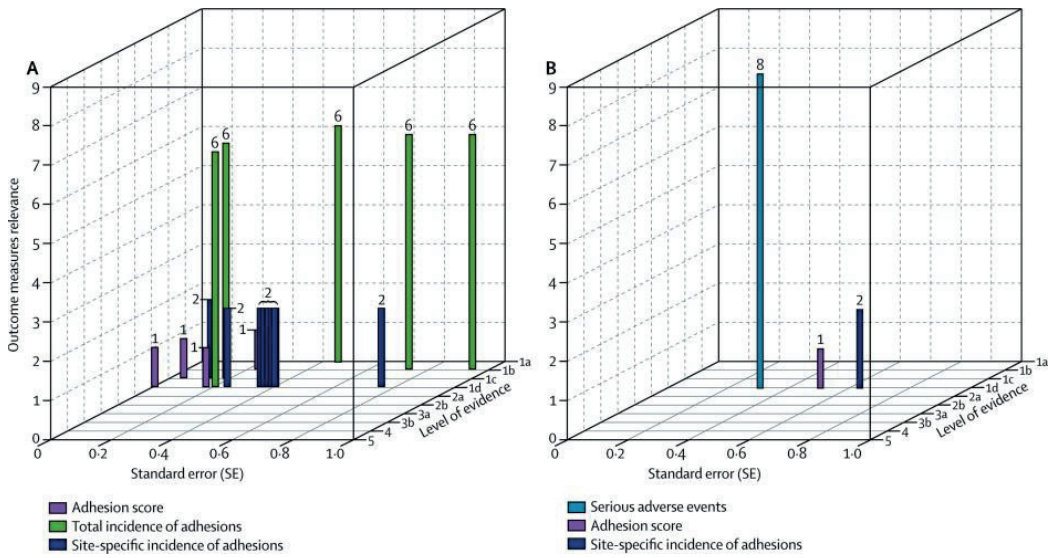


Figure 4: Outcomes of oxidised regenerated cellulose versus no adhesion barrier

Benefit (A) and no effect or harm (B). Systematic error: 1a is meta-analysis of low-bias risk randomised controlled trial, 1b a low-risk bias randomised controlled trial, 1c is meta-analysis of all randomised controlled trials, and 1d a high-risk bias randomised controlled trial. Standard error less than 0.20 is low risk for random error, 0.20–1.00 is moderate risk, and greater than 1.00 is high risk. Studies with a high risk for random error are outside the range and are considered irrelevant for decision making. Results most important for clinical decision making are the highest bars in the upper-left part of the plot.



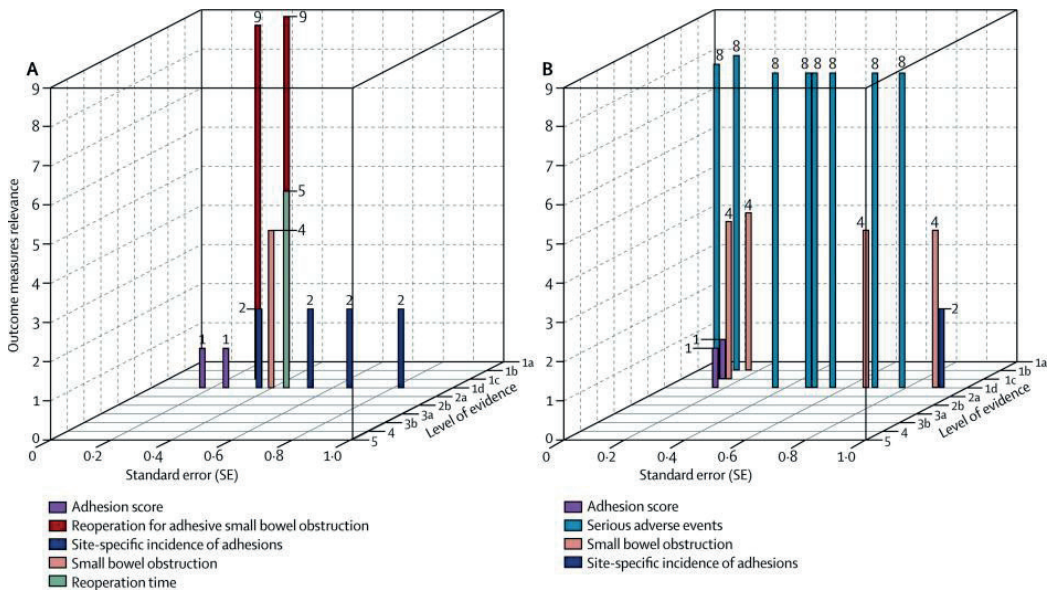
With regard to outcomes important for decision making, the overall incidence of adhesions reported by three trials (578 patients) was significantly reduced in the treatment group (RR 0.51, 95% CI 0.31–0.86; Fig 3) with a number needed to treat of 6 (95% CI 3.37–21.00). The intervention effect increased when only trials with low risk of bias were assessed. No data were available for operation time and small bowel obstruction for any cause. Use of oxidised regenerated cellulose significantly reduced the site-specific incidence of adhesions (RR 0.66, 95% CI 0.59 to 0.74) and adhesion scores (standardised mean difference [SMD] −3.74, 95% CI −5.71 to −1.77).

Hyaluronate carboxymethylcellulose is a solid adhesion barrier in the form of a thin translucent membrane. The membrane adheres well to moist tissue surfaces and forms a viscous gel in 1–2 days. The barrier is absorbed from the abdominal cavity within 7 days, and is metabolised and cleared via the kidney in a maximum of 28 days.[60]

Nine trials (3052 patients) assessed hyaluronate carboxymethylcellulose (1517 patients) compared with no adhesion barrier (1535 patients).[1,36-39,41-44] One trial had risk of low bias.[1] Three trials were investigator driven, four were sponsored by industry, and in two trials the sponsor was not specified. Six trials were of colorectal surgery and one each was of gynaecological, hepatic, and gastric surgery.

Figure 5 shows overall results for hyaluronate carboxymethylcellulose. Some evidence suggests that hyaluronate carboxymethylcellulose reduces the incidence of reoperations for adhesive small bowel obstruction. Five trials evaluated this outcome, three in colorectal surgery, and one each in hepatic and gastric surgery. Hyaluronate carboxymethylcellulose significantly reduced the incidence of reoperations for adhesive small bowel obstruction in colorectal surgery (RR 0.49, 95% CI 0.28–0.88). The difference in the incidence of reoperation related to adhesive small bowel obstruction was not significant in hepatic surgery (RR 0.13, 95% CI 0.01–2.95) and gastric surgery (RR 0.35, 95% CI 0.01–8.50). Operation time also seems to be reduced by use of hyaluronate carboxymethylcellulose.

Figure 5: Outcomes of hyaluronate carboxymethylcellulose versus no adhesion barrier
Benefit (A) and no effect or harm (B)



Seven trials studied the incidence of serious adverse events, five for colorectal surgery and one each for hepatic and gastric surgery. Differences between groups for the incidences of serious adverse events were all non-significant (figure 3).

A post-hoc analysis of one trial with low risk of bias showed that hyaluronate carboxymethylcellulose wrapped around a new bowel anastomosis seemed to result in a higher incidence of serious adverse events: abscesses, fistulas, and anastomotic leakages.[1] In more recent trials, the practice of wrapping

hyaluronate carboxymethylcellulose around anastomoses has been abandoned.[39,42] There were no data for pregnancy rate.

In one trial of hyaluronate carboxymethylcellulose investigating two-stage hepatic surgery, operation time was significantly shorter in the hyaluronate carboxymethylcellulose group at reoperation (SMD −2.30, 95% CI −3.16 to −1.43). We report no significant difference for the outcome of small bowel obstruction from any cause in either gastric or colorectal surgery.

Our meta-analysis showed that hyaluronate carboxymethylcellulose significantly reduced the incidence of site-specific adhesions (RR 0.71, 95% CI 0.54–0.95). Adhesion score was significantly reduced in one trial of gynaecological surgery (SMD −1.41, 95% CI −1.80 to −1.02), but not for colorectal surgery (−0.86, −1.96 to 0.24).

Icodextrin is a water-soluble glucose polymer derived from cornstarch. It is a liquid adhesion barrier in a 4% solution. Before the icodextrin breaks down into oligosaccharides and is metabolised, the colloidal osmotic activity causes the fluid to reside in the abdominal cavity for 3–5 days.[61,62]

Four trials (764 patients) randomly assigned patients to icodextrin (386 patients), no adhesion barrier (90 patients), or placebo (282 patients).[46-49] The study of Kössi and colleagues was unclear about whether six patients were allocated to treatment or control.[48] No trials had a low risk of bias.

Most outcome data were not included in the Manhattan plot because of the high risk of random errors (appendix). Reoperation for adhesive small bowel obstruction did not differ significantly between groups (RR 0.33, 95% CI 0.03–3.11). Icodextrin has no beneficial effects on the number of serious adverse events (Fig 3). There is evidence of a moderate risk for random error that icodextrin reduces the incidence of small bowel obstruction. There is insufficient evidence to assess whether icodextrin has a beneficial effect on the incidence of adhesions or operation time (SMD −0.48, 95% CI −1.44 to 0.49).

Incidence of serious adverse events was similar among the groups in gynaecological surgery (RR 1.00, 95% CI 0.76–1.30) and lower alimentary tract surgery (0.98, 0.63–1.52).[46,48,49] There were no data for pregnancy rate.

Overall incidence of adhesions and operation time did not differ significantly for icodextrin. Icodextrin significantly reduced the incidence of small bowel obstruction by any cause (RR 0.20, 95% CI 0.04–0.88). There were no data for incidences of site-specific adhesions and we report no significant difference for adhesion score (SMD −0.29, 95% CI −2.97 to 2.39).

The polyethylene glycol adhesion barrier consists of two liquid precursor solutions that quickly react after being sprayed in the abdomen, forming a hydrogel. One of the precursors contains a small amount of methylene blue, enabling the area covered and the thickness of the hydrogel layer to be seen during laparoscopy. The gel is degraded through hydrolysation and cleared via the kidneys in around 7–8 days.[63]

Four trials (191 patients) assessed polyethylene glycol in 111 patients and placebo in 80 patients.[53,54,55] One trial had a low risks of bias for all six bias risk domains.[55] No data were available for reoperation for adhesive small bowel obstruction. No data were available about the effect of polyethylene glycol on pregnancy rate. The incidence of serious adverse events did not differ in three trials of gynaecological surgery (RR 0.55, 95% CI 0.16–1.87) and colorectal surgery (1.11, 0.43–2.85). Groups did not differ significantly for incidence of adhesions (RR 0.78, 95% CI 0.60 to 1.01). Polyethylene glycol had a beneficial effect on operation time in one trial with a low risk of systematic error (SMD −0.84, 95% CI −1.49 to −0.19). No data were available for small bowel obstruction by any cause and incidence of site-specific adhesions.

Polyethylene glycol significantly reduced adhesion scores both in gynaecological surgery (SMD −0.71, 95% CI −1.21 to −0.22) and in one trial of colorectal surgery with low risk of bias (SMD −1.71, 95% CI −2.45 to −0.97); however, the studies assessing these outcomes had high risk of random error.

Discussion

Sufficient evidence exists to suggest that oxidised regenerated cellulose and hyaluronate carboxymethylcellulose reduce adhesion formation. There is evidence that hyaluronate carboxymethylcellulose reduces the number of reoperations for adhesive bowel obstruction and operative time. Oxidised regenerated cellulose reduces the incidence of adhesions in gynaecological surgery, but no data were available about the effect on reoperations for adhesive bowel obstruction. Icodextrin had no effect on the incidence of reoperation for adhesive small bowel obstruction in one small trial, and no data for the primary outcome were available for polyethylene glycol. None of the four barriers investigated increased serious adverse events.

28 trials had been done, which is high for surgical research. Detailed assessment of the risk of bias showed that these trials had a low risk of both systematic and random errors compared with other surgical research—eg, robotic surgery, laparoscopic cholecystectomy, and fast-track surgery.[22,64]

Despite the large number of trials, outcome comparisons included only a few trials and results per comparison can easily be dominated by a single large trial. The different types of barrier used, the large clinical heterogeneity, and the different outcome parameters reported, hinder the pooling of results from multiple trials and made subgroup analyses necessary. Therefore, we assessed the potential benefits and harm of adhesion barriers by the error-matrix approach with visualisation in a Manhattan plot. This approach has the advantage over standard forest plots that several outcomes can be integrated and shown in one figure.

Only 14 trials reported outcomes that are critical or important when considering whether to apply adhesion barriers—reoperation for adhesive small bowel obstruction, total incidence of adhesions, operation time of reoperation, and small bowel obstruction (any cause). Implementation of these

outcome measures is one of the biggest challenges in the design of trials of new adhesion barriers.[65] Completion of future trials will be challenging because of the need for many patients to assess clinically critical outcomes, multicausality of some outcomes (eg, pregnancy rate), and to provide long-term follow-up data (eg, for adhesive small bowel obstruction). The risk of publication bias cannot be fully excluded—we identified some trials that have not been published yet. However, we do not believe that results of these trials will alter conclusions: the results of unpublished studies matched those of published reports and funnel plots showed no publication bias. Most of the trials were sponsored by industry, which might have resulted in publication bias of positive results and overestimation of intervention effects. However, this effect seems unlikely because data of investigator-driven trials compare favourably with industry-sponsored trials and risk of publication bias was low.

Although serious adverse events were reported for half the trials, safety data for some barriers are scarce. Few adverse events were reported for oxidised regenerated cellulose, probably because the barrier was only studied in gynaecological surgery, in which little bleeding occurs. Previous studies showed that oxidised regenerated cellulose barriers cause an inflammatory response when in contact with blood.[66,67] Additional safety information for icodextrin comes from a large registry including over 4000 patients who had general and gynaecological surgery.[68,69] The data support the good safety profile of icodextrin.

Three Cochrane reviews have addressed adhesion prevention for gynaecological and open colorectal surgery.[14-16] The present study aggregates the evidence from these three reviews and includes additional evidence from trials of gastric and hepatic surgery as well as two trials of colorectal surgery that were missed by previous reviews.[43,55] Additionally, previous reviews did not rank different outcomes, despite the variety of consequences from a patient's perspective, and thus—for example—hiding the specific effect on adhesion incidence and type of small bowel obstruction.[14] An adhesion barrier cannot reduce the incidence of bowel obstruction secondary to tumour or hernia. In addition, we deemed operation time to be an important clinical outcome because evidence suggests that prolonged adhesiolysis increases the risk of inadvertent organ injury.[5,56] Compared with previous reviews, we did a more comprehensive and clinically meaningful analysis, which included risk of bias, risk of random error, a grey literature search, and an analysis of the role of sponsorship. The error matrix approach provides more detailed and clearer evidence of benefit and harm of an intervention. As more studies are done, clinical evidence increases and becomes more difficult to overview. The Manhattan plot helps to judge the relevance and strength of the evidence available for each specific adhesion-related outcome for a single intervention.

Oxidised regenerated cellulose reduces adhesion formation in fertility surgery. The implications for clinical practice remain unclear because none of the trials assessed pregnancy rate. With regard to

the robustness of data for prevention of adhesion formation and safety, future studies should assess whether oxidised regenerated cellulose reduces reoperation-associated complications.

Hyaluronate carboxymethylcellulose reduces operation time in two-stage liver surgery and has a modest reduction effect on adhesive small bowel obstruction. The number needed to treat to prevent one case of adhesive small bowel obstruction is high for this rare but potentially life-threatening complication of general and gynaecological surgery. However, routine use in high-risk surgeries for bowel obstruction is warranted on the basis of our efficacy and safety results. We expect that with increasing evidence on clinical and socioeconomic effect of adhesiolysis, the use of hyaluronate carboxymethylcellulose to prevent organ injury during repeated open surgery will spread.[5,56]

Indications for the use of an adhesion barrier also depend on its formulation. Both oxidised regenerated cellulose and hyaluronate carboxymethylcellulose are solid barrier films and difficult to apply during laparoscopic surgery. Icodextrin and polyethylene glycol are easier to apply at laparoscopy. Formulation could also affect efficacy and adverse events. The solid and viscous gel barriers are thought to be more effective at preventing adhesion at sites of severe peritoneal injury and adhesiolysis, whereas liquid barriers provide better protection for injured surfaces—eg, by retractors or desiccation—distant from the region of surgical dissection. However, no clear evidence supports this hypothesis. Two adhesion barrier gels based on hyaluronic acid were associated with serious adverse events.[19] We doubt whether the gel formulation contributed to these adverse events because the hyaluronate carboxymethylcellulose film also becomes gelatinous after application. More likely, chemical adjuvants—the ferric ions—increase adverse tissue reactions.[70]

Results from our study could be used to develop guidelines for the use of barriers to prevent adhesion-related complications. Thus far, guidelines are only available for gynaecological surgery.[71]

Acknowledgments

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7

Adhesion barrier in colorectal surgery: modeling of cost-effectiveness

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Abstract

Background

Adhesion barriers are proven effective reducing adhesion-related complications after colorectal surgery. However, mostly for financial reasons, barriers are seldom applied. Aim of this study was to determine the cost-effectiveness of an adhesion barrier in colorectal surgery.

Methods

A decision tree model was developed to determine the cost-effectiveness using an adhesion barrier in colorectal surgery based on the best available evidence. Current practice (no adhesion barrier) was compared with using an adhesion barrier in open and laparoscopic colorectal surgery. Outcomes of the model were incidence of clinical consequences of adhesions, direct healthcare costs, and the incremental cost effectiveness ratio (ICER) representing the costs per patient with adhesions prevented. Uncertainty was addressed in deterministic and probabilistic sensitivity analyses.

Results

An adhesion barrier reduces the incidence of adhesions from 88.9% to 45.3% in open and 62.3% to 31.8% in laparoscopic colorectal surgery, and the incidence of ASBO from 8.6% to 5.8% and 6.6% to 4.5%. The adhesion barrier slightly reduces costs in open colorectal surgery when compared with no adhesion barrier ($4372 versus $4474). Using an adhesion barrier in laparoscopic procedures led to an increase in costs of $41 ($4220 versus $4179). The ICER for one patient was $135 for the laparoscopic cohort. Probabilistic sensitivity analysis showed a 65% and 37% probability of an adhesion barrier being cost-reducing for open and laparoscopic surgery, respectively.

Conclusion

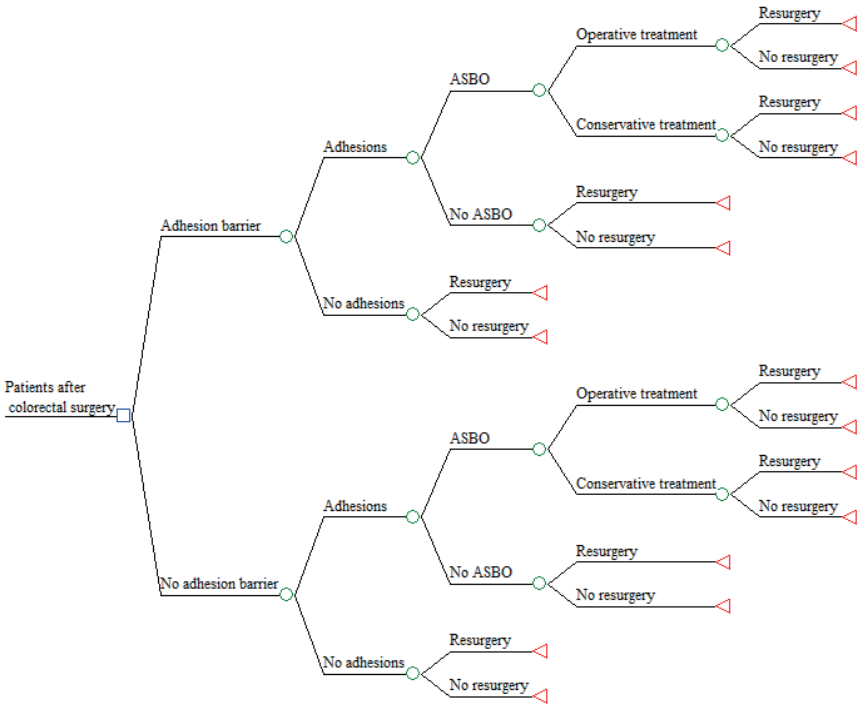
The use of adhesion barriers in open colorectal surgery is cost-effective preventing adhesion related problems. In laparoscopic colorectal surgery, an adhesion barrier is effective at low costs.

Introduction

Colorectal surgery commonly induces postoperative adhesion formation, causing a lifelong risk for small bowel obstruction, female infertility, and chronic visceral pain.[1-4] Lysis of adhesions at reoperative surgery is associated with inadvertent organ injury, prolonged operative time and an increased risk of postoperative complications and therefore higher costs.[5-7] Several adhesion barriers are developed to prevent postoperative adhesion formation after abdominal surgery. In a recent systematic review and meta-analysis on efficacy and safety of adhesion barriers, hyaluronate carboxymethylcellulose (HA/CMC) was proven to safely reduce the incidence of site specific adhesions, and the incidence of reoperations for adhesive small bowel obstruction after open colorectal surgery.[8] Despite the burden of postoperative adhesions and the proven benefit of adhesion barriers, these are seldom applied. In a nationwide survey in 2009 in The Netherlands only 13.4% of surgeons indicated to have used any adhesion barrier in the previous year, and a recent follow-up survey did not show much change (unpublished data).[9] Doubts about cost-effectiveness and the need for adhesion prevention in minimally invasive surgery may explain the reluctance using barriers. Previous cost effectiveness analyses of adhesion barriers are based on costs of adhesion-related readmission, and only concern open surgery.[10,11] The efficacy data used were derived from second-look surgery studies, suggesting an approximate 25-50% reduction in the number or density of adhesions with the use of a barrier. In the absence of data on reduction of adhesion-related readmissions with the use of a barrier, costs were extrapolated from the reduction of adhesions. Since publication of these analyses evidence on both the burden of adhesions and the effectiveness of adhesion barriers has increased substantially. Earlier, readmission for postoperative small bowel obstruction was considered the most important complication.[12] New evidence makes clear that difficulty due to dissecting adhesions at repeat abdominal surgery is an even bigger problem.[13] Moreover, evidence on efficacy of adhesion barriers is no longer limited to adhesion incidence, but comprises clinically relevant endpoints.[8]

We developed a decision model for the use of an adhesion barrier in open and laparoscopic colorectal surgery, based on the best available evidence considering cost and effect. With this model we aim making an important step to an evidence based decision on the use of adhesion barriers in colorectal surgery.

Figure 1: Decision tree model for evaluation of the use of an adhesion barrier in colorectal surgery.



Methods

Decision model

We designed a decision tree model using Microsoft Office Excel 2007, evaluating the strategy of adhesion prevention with an adhesion barrier in open and laparoscopic colorectal surgery. A decision model is a simplified framework of complex real-life processes, using a mathematical method to weigh risks, benefits, and costs of clinical strategies.[14] In the model two strategies are compared: (1) current clinical practice; colorectal surgery without the use of an adhesion barrier; (2) colorectal surgery with the use of an adhesion barrier (figure 1). Hypothetical cohorts of patients undergoing colorectal surgery, open or laparoscopic, are distributed over the different pathways in the decision tree, based on a set of probabilities that were derived from recently published systematic reviews, and observational and intervention studies. This allowed us to synthesize evidence and thereby to evaluate effects and adhesion related health care costs determined by treatment decision.

Adhesive small bowel obstruction (ASBO) and difficulties at reoperation were included in the model

as potential consequences of adhesions. Female infertility and chronic visceral pain were not considered. Risk for infertility will only be an additional reason for the use of an adhesion barrier in a very small and specific subgroup. Regarding chronic visceral pain no consistent evidence is available on etiology, incidence and costs after colorectal surgery.[4]

Population

The two target populations consist of patients undergoing a colorectal resection, either by open or laparoscopic approach. Colorectal resection is commonly performed and for various indications; the main indication being colorectal cancer.[15] Colorectal surgery has a relatively high incidence of postoperative adhesion formation.[13,16] In 2014 over 65% of colorectal cancer resections in the Netherlands were performed by laparoscopic technique.[17] There is recent evidence that laparoscopy is associated with a lower incidence of adhesions, particularly to the abdominal wall (unpublished data).[18]

Probabilities

In the model hypothetical cohorts of patients undergoing a colorectal resection, with or without the use of an adhesion barrier, have different probabilities for the development of adhesions, and subsequent development of ASBO, operative or conservative treatment for ASBO, and adhesiolysis at future repeat surgery. Probability estimates were derived from recent literature (see table 1).[8,19-30] Risk ratios for adhesions, ASBO and operative treatment of ASBO with the use of an adhesion barrier are based on efficacy data for HA/CMC, since this is the only adhesion barrier with consistent evidence available on adhesion prevention in visceral surgery. Although HA/CMC is not easily applicable in laparoscopic surgery and evidence for laparoscopy is lacking, we extrapolated the efficacy data of HA/CMC in open colorectal resection to the laparoscopic model. The data on incidence of adhesions after open and laparoscopic colorectal surgery were derived from a multicentre study that has been submitted for publication, (clinicaltrials.gov registration number: NCT01720966). In this study adhesions after open and laparoscopic colorectal cancer surgery are compared at surgery for liver metastases. In the recent systematic review on the value of adhesion barriers there were no data on total incidence of adhesions with the use of HA/CMC.[8] A new search yielded no additional data on total incidence of adhesions with the use of HA/CMC. Thus, adhesion incidence with HA/CMC was derived from the incidence of site-specific adhesions reported, i.e. midline, pelvic adhesions, only including the anatomical site with the highest incidence of adhesions from each study.[19-21] The peristomal site was considered not relevant for total adhesion formation after colorectal surgery. The efficacy is expressed as a risk ratio of adhesions with the use of HA/CMC versus no barrier (RR 0.51 [95% CI 0.43-0.61]).

Table 1: Input probabilities in decision tree model.

	Open			Laparoscopic				Adhesion barrier strategy		
Variable	**Probability**	**α**	**β**	**Probability**	**α**	**β**	**Source**	**RR**	**95%CI**	**Source**
Patients with adhesions	0.889	80	10	0.623	38	23	Unpublished data	0.51	0.43-0.61	[19-21]
Patients with ASBO 4 years	0.0856	199	2127	0.0663	77	1085	[22-29]	0.68	0.35-1.32	[13]
Patients with ASBO treated surgically	0.032	74	2252	0.031	36	1126	[22-29]	0.49	0.28-0.88	[13]
Patients with repeat surgery 4 years	0.208	64	200	0.209	64	200	[22-30]			

α = patients with event; β = patients without event; RR = relative risk; CI = confidence interval; ASBO = adhesive small bowel obstruction

The probability of ASBO and the probability of surgery for ASBO after colorectal surgery, were derived from an update (1990 - June 2016) of the systematic review on the burden of adhesions after abdominal surgery.[22-29] Weighted mean follow-up of the studies was 55.3 months. The probability of future repeat abdominal

surgery was derived from a recently published, prospective cohort of patients who underwent elective abdominal surgery.[30] In four years after initial lower gastrointestinal tract surgery, 24% of patients underwent repeat abdominal surgery, including reoperations for ASBO. In the model reoperations for ASBO were subtracted from the probability for repeat surgery avoiding that these reoperations are two times included in the model.

Costs

An analysis of adhesion related costs was performed with a healthcare perspective, including only direct healthcare costs for treatment (table 2). All monetary values are presented in US dollars (USD). Euro was converted to US dollars using the exchange rate 1 Euro:1.1264 USD.

The mean numbers of films per patient reported in two of the three studies on adhesion prevention with HA/CMC in colorectal surgery was 3.3 films. The total costs for HA/CMC were based on the use of 3.3 films and the price of a HA/CMC film in the Netherlands, adding up to a total cost of $629.68.[19-31]

There was no recent literature available on costs of ASBO. To evaluate the healthcare costs of ASBO, all patients admitted from November 2013 to October 2015 to Radboud University Medical Center with the diagnosis ASBO were retrospectively analyzed to assess the costs of these admissions (n=39). Mean costs of an admission for ASBO with operative treatment (n=19) was $18.124,77 (SD $2.822,22). For non-operative treatment (n=20) mean costs were $2.565,12 (SD $298,88).

The costs for repeat surgery were derived from a recent large cohort study on adhesiolysis-related morbidity in abdominal surgery.[5]

Table 2: Costs used in the model.

	Value	SD	Source
Costs HA/CMC	$ 630		[19,21]
ASBO with operative treatment	$ 18,125	$2,822	Radboud University Medical Centre
ASBO with non-operative treatment	$ 2,565	$ 299	Radboud University Medical Centre
Repeat surgery no adhesions	$ 14,063	$ 812	[5]
Repeat surgery adhesions	$ 18,579	$ 1,722	[5]

SD = standard deviation

Data analysis

Data were analyzed using mean values for a base case analysis, to obtain percentage of ASBO, reoperation for ASBO, and patients with adhesions, and direct healthcare costs for the two strategies in four years following colorectal surgery. The time frame was based on the mean four years' follow-up periods of the studies underlying the probabilities for ASBO and repeat surgery. If the use of an adhesion barrier was more effective and more expensive, incremental cost-effectiveness ratios (ICER) were calculated to determine the additional costs for one patient with adhesions prevented. In case the adhesion barrier strategy was more effective and cost-reducing, this was considered dominant and ICERs were not calculated. A base case analysis was conducted for the two strategies in open and laparoscopic surgery separately.

Probabilistic sensitivity analysis was performed, using Monte Carlo simulation, to explore the impact of uncertainties in the model parameters, shown in table 1 and 2. In the Monte Carlo simulation 5,000 samples were drawn from the parameter distributions. For each sample, the hypothetical cohort runs through the model based on these sampled parameters, representing the uncertainty in

the cost-effectiveness estimation. Lognormal distributions were used for all risk ratios, beta distributions for probabilities, and costs were described by normal distributions.

In addition, threshold analyses were conducted for the costs of the adhesion barrier and the probability of repeat surgery. Deterministic sensitivity analysis was conducted to explore influence of deviation in the efficacy of the adhesion barrier on the cost-effectiveness, assuming all other variables to be fixed. The efficacy of the adhesion barrier was changed to a best- and worst case scenario. For the worst case scenario the risk ratios for adhesions, ASBO, and operative treatment of ASBO were all set to the upper limit of their confidence interval (table 1). For the best case scenario all risk ratios were raised to the lower limit of their confidence interval.

Results

Base case analysis

Taking the parameters at their base case values, for the open cohort the adhesion barrier strategy was both more effective and less expensive than the no adhesion barrier strategy, while in the laparoscopic cohort the adhesion barrier strategy was more effective, but more expensive (table 3). In open colorectal surgery the percentage of patients with adhesions reduced from 88.9% to 45.3%, and ASBO incidence from 8.6% to 5.8% with an adhesion barrier. The expected mean direct healthcare costs in four years after initial open colorectal surgery were reduced in the adhesion barrier group with $102, from $4474 in the group without an adhesion barrier to $4372. After laparoscopic colorectal surgery the rate of patients with any adhesions was reduced from 62.3% to 31.8%, and ASBO incidence from 6.6% to 4.5% with an adhesion barrier. Costs increased with $41 when an adhesion barrier was used. Direct health care costs over four years after laparoscopic surgery for the adhesion barrier group were $4220 versus $4179 for the no adhesion barrier group. In open colorectal surgery the adhesion barrier strategy dominated the current no-adhesion barrier practice. For laparoscopic colorectal surgery the ICER for one patient with adhesions prevented was $135.

Sensitivity analysis

The results of the probabilistic sensitivity analysis are shown in figure 2a and b. Monte Carlo Simulation showed that the use of an adhesion barrier is always more effective for preventing adhesions or ASBO, for both open en laparoscopic surgery. The use of an adhesion barrier had a 62% probability of being cost-reducing in the open cohort. In the laparoscopic cohort the probability was 35%.

Table 3: Results of base case and deterministic sensitivity analyses.

Strategy	Costs	Percentage adhesions	Percentage ASBO	Costs per patient with adhesions prevented
Open cohort				
Baseline				
No barrier	$4474	88.9%	8.6%	
Barrier	$4372	45.3%	5.8%	Dominant
Best case scenario				
No barrier	$4474	88.9%	8.6%	
Barrier	$4129	38.2%	3.0%	Dominant
Worst case scenario				
No barrier	$4474	88.9%	8.6%	
Barrier	$4789	54.2%	11.3%	$908
Laparoscopic cohort				
Baseline				
No barrier	$4179	62.3%	6.6%	
Barrier	$4220	31.8%	4.5%	$135
Best case scenario				
No barrier	$4179	62.3%	6.6%	
Barrier	$4016	26.8%	2.3%	Dominant
Worst case scenario				
No barrier	$4179	62.3%	6.6%	
Barrier	$4576	38.0%	8.7%	$1,663

Threshold analysis in the open cohort showed that using a barrier priced at $732 or more does no longer reduce costs. The same effect was seen with the reoperation rate set to 15% or less. In the laparoscopic cohort the thresholds for cost-reduction with an adhesion barrier were a price of $589 and a reoperation rate of 25%.

Results of the deterministic sensitivity analysis are shown in table 3. In the best case scenario, applying an adhesion barrier in both open and laparoscopic colorectal surgery reduces costs. In the worst case scenario the ICER for one patient with adhesions prevented is $908 in the open and $1,664 in the laparoscopic cohort.

Figure 2a: Scatterplot of Monte Carlo simulation for open colorectal surgery displaying cost (y-axis) and effect (x-axis) of adhesion barrier strategy.

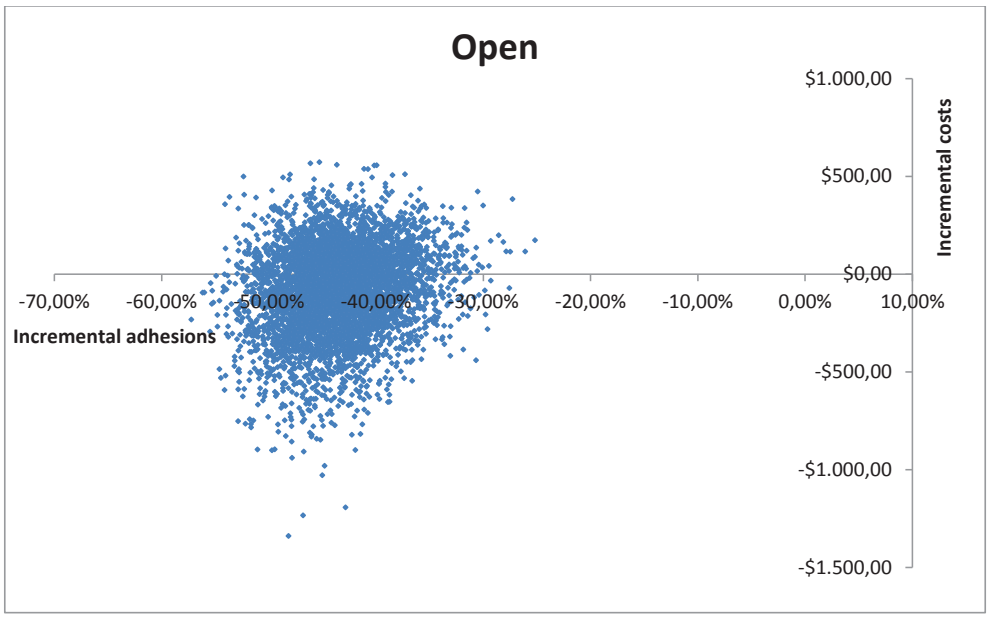
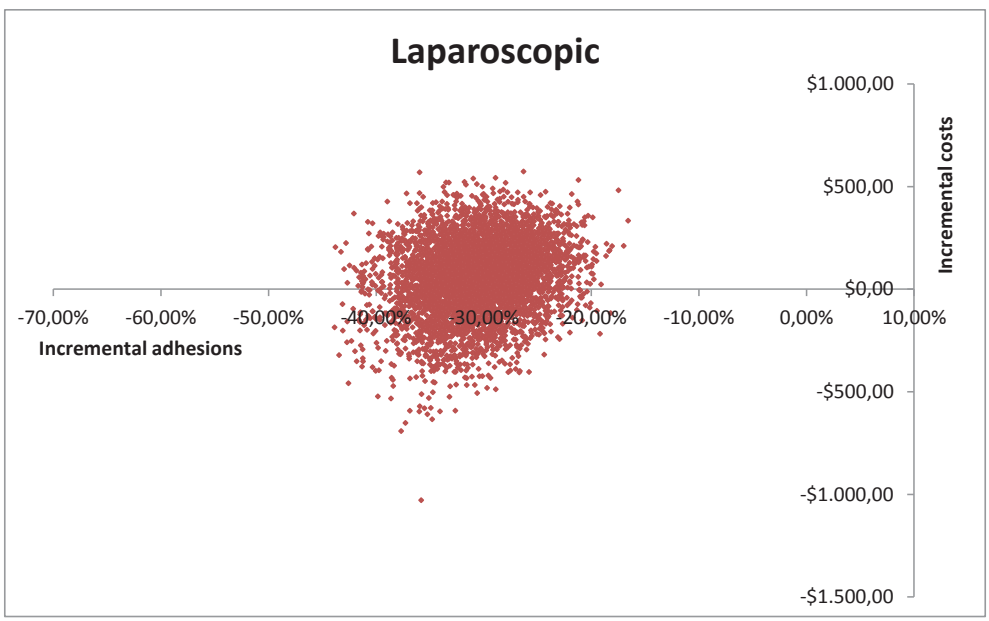


Figure 2b: Scatterplot of Monte Carlo simulation for laparoscopic colorectal surgery displaying cost (y-axis) and effect (x-axis) of adhesion barrier strategy.



Discussion

An adhesion barrier in open and laparoscopic colorectal surgery can effectively reduce adhesions, adhesive small bowel obstruction and adhesion-related problems at repeat abdominal surgery. Considering a four-year time frame, using an adhesion barrier reduces costs in open colorectal surgery, while in laparoscopic colorectal surgery the expenses are a little over $40 per patient and the additional costs for one patient with adhesions prevented are $135.

The findings in the present study are in agreement with a comparable study, that demonstrated cost savings in open, all types, abdominal surgery, and potential cost-effectiveness in major laparoscopy.[32] Our study has the advantage that it concerns a homogenous group of patients with a high risk of postoperative adhesion formation. This well-defined population enhances the clinical applicability of the results. Also, more recent cost data are used in the present model of which the majority was specific for colorectal surgery. Costs are twice as much for operative treatment of ASBO and for the adhesion barrier compared to costs reported previously. A comparable underestimation of costs for the adhesion barrier and ASBO treatment was found in other cost-effectiveness reports early this century.[10,11] The most important limitation of previous studies is the lack of evidence on efficacy of the adhesion barrier reducing adhesion-related complications.

The major strength of the present study is that recently generated evidence for the burden of adhesions and the efficacy of adhesion barriers in colorectal surgery could be synthesized. Limitation is the necessity of extrapolating data from open to laparoscopic colorectal surgery due to scarce and inconsistent evidence with other formulas of HA/CMC (e.g. slurry made of film and spray) in laparoscopy.[33-35] A deviating efficacy in laparoscopy would be highly relevant especially because the majority of colorectal resections are being performed by laparoscopy.[17] In the deterministic sensitivity analysis assumed worse effectiveness of the adhesion barrier (RR 0.61) resulted in an ICER of $908 in the open and $1,663 in the laparoscopic cohort, which for laparoscopy is more than a ten-fold increase compared to base case analysis.

The time frame to which the model applies was limited to four years, while adhesion related complications or repeat surgery may occur many years later.[12] However, approximately 70% of ASBO occurs within the first 4 years after lower abdominal surgery; regarding repeat surgery there is no data available. Using a longer time frame would increase ASBO and repeat surgery rate, thereby potentially increasing the clinical benefit and cost-effectiveness of the adhesion barrier strategy.

Female infertility and chronic visceral pain, which are known consequences of adhesions, were not included in the model. Risk for infertility is only applicable to a small and specific group of patients undergoing colorectal surgeries at young age. Regarding chronic visceral pain no consistent evidence is available, and most costs are generated outside the hospital.[4] The incompleteness of the model for

these adhesion-related complications may have caused underestimation of adhesion-related costs and thus an underestimation of the cost-effectiveness of the use of adhesion barriers.

The model took into account the costs of repeat surgery depending on presence and not extent and severity of adhesions. Evidence shows that laparoscopic approach and use of an adhesion barrier reduce adhesions' incidence, extent and severity (unpublished data).[8] Although reduction of extent and severity of adhesions potentially decreases adhesiolysis-related complications and costs, evidence is insufficient to consider including these variables in the model.[5] Excluding the efficacy and costs related to reduction in severity and extent may have resulted in an overestimation of the adhesion related costs in the laparoscopic cohort, and an underestimation of the benefit of an adhesion barrier in both cohorts.

Due to a higher life expectancy and advances in surgical technology, an increasing number of patients undergo abdominal surgery multiple times during lifetime.[30] Adhesion formation is the most common long term complication of abdominal surgery, and preventing adhesion formation from initial abdominal surgery is the critical step in breaking the sequence of complications due to adhesions. Despite evidence of reduced adhesion formation when applying adhesion barriers, adhesion barriers are seldom used in practice. Doubts about cost-effectiveness and the need for adhesion prevention in the minimally invasive era probably underlie this reluctance.[9] The present cost-effectiveness analysis is based on best available evidence for both open and laparoscopic colorectal surgery and can at least for open colorectal surgery take away these doubts. Since the use of an adhesion barrier in laparoscopic colorectal surgery involves extra costs, data on quality-adjusted life-years (QALYs) are required to assess willingness to pay.[36] In order to determine QALYs for adhesions and the use of adhesion barriers, future research should address patient reported outcomes (PROs), such as functional status and quality of life. It is conceivable that adhesion-related complications such as ASBO, reoperation associated complications, and chronic visceral pain will have a negative impact on PROs.[37]

It is concluded that adhesions, adhesive small bowel obstruction and adhesion-related problems at repeat abdominal surgery can effectively be reduced with the use of an adhesion barrier in both open and laparoscopic colorectal surgery. For open colorectal surgery this will probably result in cost savings, and for laparoscopic colorectal surgery this might be accompanied by limited costs.

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8

Efficacy and safety of the C-Qur™ Film Adhesion Barrier for the prevention of surgical adhesions (CLIPEUS Trial): study protocol for a randomized controlled trial

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Abstract

Background

Adhesions develop in more than 90% of patients undergoing an intra-abdominal surgical procedure. Adhesion barriers are rarely used despite the high morbidity caused by intra-abdominal adhesions. Only one of the currently available adhesion barriers has demonstrated consistent evidence for reducing adhesions in visceral surgery. This agent has limitations through poor handling characteristics because it is sticky on both sides. C-Qur™ Film is a novel thin film adhesion barrier and it is sticky on only one side, resulting in better handling characteristics. The objective of this study is to assess efficacy and safety of C-Qur™ Film to decrease the incidence of adhesions after colorectal surgery.

Methods/Design

This is a prospective, investigator initiated, randomized, double-blinded, multicenter trial. Eligible patients undergoing colorectal resection requiring temporary loop ileostomy or loop/split colostomy by laparotomy or hand assisted laparoscopy will be included in the trial. Before closure, patients are randomized 1:1 to either the treatment arm (C-Qur™ Film) or control arm (no adhesion barrier). Patients will return 8 to 16 weeks post-colorectal resection for take down of their ostomy. During the ostomy takedown, adhesions will be evaluated for incidence, extent, and severity. The primary outcome evaluation will be assessment of adhesions to the incision site. It is hypothesized that the use of the C-Qur™ Film underneath the primary incision reduces the incidence of adhesion at the incision by 30%. To demonstrate a 30% reduction in the incidence of adhesions, a sample size of 84 patients (32 + 10 per group (25% drop out)) is required (two-sided test, $\alpha = 0.05$, 80% power).

Discussion

Results of this study add to the evidence on the use of anti-adhesive barriers in open and laparoscopic 'hand-assisted' colorectal surgery. We chose incidence of adhesions to the incision site as primary outcome measure since clinical outcomes such as small bowel obstruction, secondary infertility and adhesiolysis related complications are considered multifactorial and difficult to interpret. Incidence of adhesions at repeat surgery is believed to be the most valuable surrogate endpoint for clinically relevant adhesion prevention, since small bowel obstruction and adhesiolysis at repeat surgery are not likely to occur when complete adhesion reduction in a patient is accomplished.

Trial registration

ClinicalTrials.gov Identifier NCT01872650, registration date 6 June 2013.

Background

Postoperative adhesions develop in more than 90% of patients undergoing an intra-abdominal surgical procedure.[1] These adhesions are known to cause small bowel obstruction, secondary infertility and pain.[2-4] At repeat abdominal surgery, intra-abdominal adhesions necessitate adhesiolysis, leading to increased operating times and substantial risk of intra- and postoperative complications.[5,6] The clinical implications of adhesions carry a significant health and socioeconomic burden.[7,8]

Adhesions are fibrous bands that connect tissue surfaces where anatomical connections do not normally exist. Adhesions are formed after a tissue surface has been injured (abrasion, desiccation, dissection, *etcetera*) and the subsequent process of fibrinolysis is incomplete.[9] At present, there are several products on the market to combat postsurgical adhesion formation. These are broad coverage adhesion barriers, generally consisting of liquids, like icodextrin 4% (Adept™, Baxter, Deerfield, IL, USA) adhesion reduction solution. These materials may limit adhesion formation by minimizing tissue insult during the surgical procedure when used as an intra-operational lavage. At the conclusion of the surgical procedure, instillation of large volumes of liquid acts to separate tissue surfaces by hydroflotation, limiting tissue-tissue contact. Broad coverage adhesion prevention has the distinct advantage of allowing the surgeon to treat many areas of the intraperitoneal space at once. A disadvantage is the lack of control giving adhesion prevention at sites at risk for complications of adhesion prevention such as an anastomosis. In addition, side effects of abdominal distension and vulvar swelling are commonly encountered in the use of liquids.[10] The second group of barriers consists of local coverage adhesion barriers: films, sprays, or gels that are applied directly to adhesiogenic tissue surfaces to act as a physical barrier that blocks tissue-tissue contact. The barrier is generally only effective when it remains at the site of treatment. This requires the barrier to either be sutured or glued in place or to have tissue adherent properties. All local coverage adhesion barriers require the surgeon to anticipate where adhesions are likely to occur and to apply the barrier directly to those sites. These generally include sites where the peritoneum was interrupted during the surgical procedure, such as under a laparotomy incision to minimize adhesions between the incision site and the viscera.[11]

Despite the frequent occurrence of adhesions after surgery and the availability of different adhesion barriers, these barriers are rarely used by general surgeons. This discrepancy might be explained by an underestimation of the impact of adhesions.[12] Also, of all the clinically available adhesion barriers, only HA/CMC (hyaluronate/carboxymethylcellulose) barrier film (Seprafilm**™,** Sanofi, Paris, France) has demonstrated consistent evidence for reducing adhesions in visceral surgery. Seprafilm**™** has limitations through poor handling characteristics because it is sticky on both sides. In a large, prospective, randomized controlled multicenter study on the safety of Seprafilm™, significantly more

anastomotic leak and leak-associated complications occurred in the Seprafilm™ group due to the wrapping of Seprafilm™ around an anastomosis.[13] A subgroup analysis of control patients and patients without (593 patients) Seprafilm™ wrapped around the anastomosis showed no significant difference. Therefore, wrapping the suture or staple line of a fresh bowel anastomosis should be avoided.

Atrium (Atrium Medical Corporation, Maquet Gentinge Group, Hudson, NH, USA) has developed and manufactures C-Qur™ Film Adhesion Barrier, a novel thin film adhesion barrier for intraperitoneal use in general surgeries. The C-Qur™ Film has been approved for use in humans and received a CE mark on 13 May 2011 (CE number 10123365). The evidence on efficacy and safety of the C-Qur film originates from research on the C-Qur mesh, a mesh with an omega-3 fatty acid coating used for patients with an abdominal ventral hernia. The C-Qur mesh was found to be safe in intraperitoneal use and reduces adhesions to the mesh.[14] The C-Qur™ Film falls into the category of local coverage adhesion barriers. The C-Qur™ Film is an adhesion barrier consisting of a non-adhesive omega-3 fatty acid layer on one side and a Na-CMC (sodium-carboxymethylcellulose) tissue adherent coating on the other side. It is fully resorbable and designed to adhere to the site of treatment for a time that is sufficient to minimize postsurgical adhesion formation and clearance from the site of treatment within approximately 60 days. In contrast to Seprafilm™, The C-Qur™ Film is a one-sided adherent, resulting in good handling characteristics. It offers the potential patient benefits of reduced adhesion formation and corresponding reduction of small bowel obstruction, secondary infertility, pain and adhesiolysis at repeat surgery. The aim of this study is to assess the efficacy and safety of C-Qur™ Film to decrease the incidence of adhesions after colorectal surgery.

Methods/Design

The CLIPEUS trial is registered with the ClinicalTrials.gov Identifier NCT01872650. The protocol was ethically approved by the official Independent Review Board Nijmegen (2013/470) and registered nationally (NL45940.091.13).[15]

Design

The CLIPEUS trial is a prospective, investigator-initiated, randomized controlled, double-blinded, multicenter trial. Treatment with the C-Qur™ film adhesion barrier will be compared with no treatment with an adhesion barrier in patients undergoing colorectal surgery with temporary diverting ostomy. The surgeons who have agreed to participate in the study and perform the index procedures will be trained in the placement of C-Qur™ Film and in adhesion mapping.

Patients will be included at the outpatient clinics of the participating centers (Radboud University Medical Center, Nijmegen; Catharina Hospital, Eindhoven; Atrium Medical Center, Heerlen; Maxima

Medical Center, Veldhoven; Gelderse Vallei Hospital, Ede) by the treating surgeons. During the operation, when the definite decision to create a temporary ostomy is made, patients are randomized 1:1 to either the treatment arm (C-Qur™ film) or the control arm (standard treatment: no adhesion barrier, no placebo). In patients assigned to the treatment arm, the C-Qur™ Film must be applied beneath the incision. The C-Qur™ film can also be applied to other areas considered to be adhesiogenic (for example, the dissection site and ostomy site, but not around the anastomosis). The number of C-Qur™ Film sheets placed is limited to a maximum area of coverage of 774 cm^2 (Table 1). Patients will return 8 to 16 weeks post-colorectal resection to have their diverting ostomy taken down. During the takedown, the incidence, extent and severity of the adhesions will be evaluated.

Table 1: Maximum area of coverage and number of sheets

Code	Size (cm)	Maximum	
		Area (cm^2)	Number of sheets
32024	7.5 × 10.0	774	10
32025	7.5 × 12.5	774	8
32029	10.0 × 10.0	774	7
32031	12.5 × 15.0	774	4

Patients

Patients aged 18 years or older who require open or hand-assisted laparoscopic colonic or rectal resection for colorectal disease with the formation of a temporary diverting loop ileostomy or colostomy and a planned closure within 8 to 16 weeks and who visit the outpatient clinic at one of the participating centers will be invited to participate in this trial.

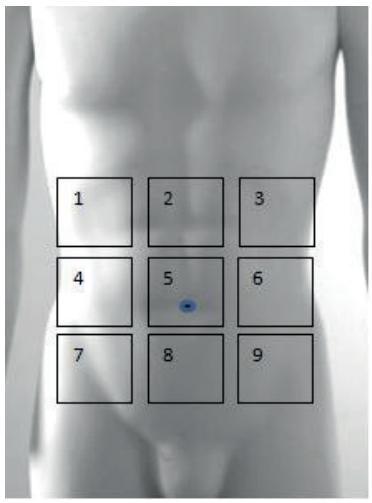
Inclusion criteria are an incision of 6 cm or longer in case of hand-assisted laparoscopy and signed informed consent.

Exclusion criteria include the following: pregnancy, patients for whom it is known prior to the initial procedure that loop ileostomy or colostomy closure between 8 and 16 weeks is not feasible, active intra-abdominal infection such as peritonitis, abdominal abscess, anastomotic leakage or fistula (interloop abscess in the resection specimen is not an exclusion criterion), endometriosis, known allergies to any component of the C-Qur Film device, an additional procedure at the time of loop ileostomy or colostomy takedown deemed interfering with adhesion assessment by the treating surgeon, intended use of intraoperative lavage/irrigation with any anti-adhesion solutions other than lactated ringers and/or saline (for example, dextran, heparin, corticosteroids, icodextrin, any other irrigant that is believed to have anti-adhesion properties) or an adhesion barrier other than C-Qur Film™, (planned) administration of systemic agents with the intention to prevent adhesion formation

within 30 days prior to the index procedure, planned chemotherapy and/or abdominal radiotherapy between index surgery and loop ileostomy or colostomy takedown, use of immune system suppressants deemed by the surgeon to interfere with wound healing (patients taking daily doses of corticosteroids exceeding 20 mg within the prior 30 days are to be excluded; patients requiring perioperative corticosteroid supplementation are not to be excluded), impaired immune system function or coagulation disorders deemed by the surgeon to interfere with wound healing, a known history of severe multiple drug allergies, a life expectancy of less than 6 months because of a medical condition or disease state, a medical condition or other serious condition that will interfere with compliance and/or ability to complete this study protocol or patients who in the opinion of the investigator would not be a good candidate for enrolment, or participation in a study of another investigational device or drug.

Figure 1: Segments of the abdominal wall and segments of the abdominal cavity. **a.** The nine segments of the abdominal wall; **b.** The ten segments of the abdominal cavity.

a.



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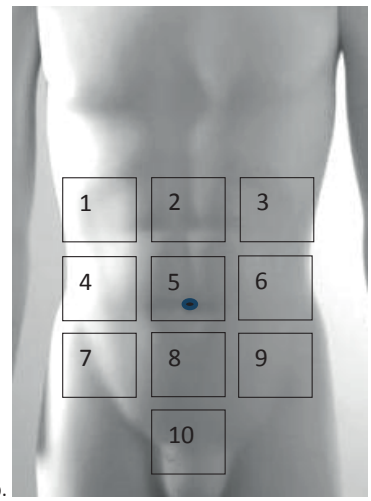

Intervention

All patients will undergo a colorectal resection with the creation of a temporary loop ileostomy or loop or split colostomy. During this index operation, adhesions, if any, will be mapped. The incidence, location, extent and severity and any treatment of adhesions will be noted. For quantifying the extent of adhesions to the abdominal wall and between organs, the abdominal wall is divided into nine segments and the abdominal cavity into ten segments (Figure 1). Severity of the adhesions will be classified according to the Zühlke classification (Table 2).[16] Classification of operative wounds based on degree of microbial contamination, number of serosal injuries and number of inadvertent

Table 2: Adhesion classification system according to Zühlke [16]

Score	Observation
0	No adhesions
1	Adhesions that are filmy and easy to separate by blunt dissection
2	Adhesions where blunt dissection is possible but sharp dissection necessary, beginning vascularization
3	Lysis of adhesions possible by sharp dissection only, clear vascularization
4	Lysis of adhesions possible by sharp dissection only, organs strongly attached with severe adhesions, damage of organs hardly preventable

enterotomies will also be noted in the source notes and CRF (case report form).

For patients randomized to the C-Qur™ Film arm, the C-Qur™ Film must be applied to the viscera underneath the primary or specimen retrieval incision in case of hand-assisted laparoscopy. Preferably, the C-Qur™ Film is also applied to other areas considered to be adhesiogenic, such as the peritoneal dissection planes and the ileum or colon at the ostomy site. The number of C-Qur™ Film sheets placed in the abdomen is limited to a maximum area of coverage of 774 cm^2. In case sheets of the largest size (15 cm × 12.5 cm) are used, the maximum is four sheets (Table 1). The application of C-Qur™ Film directly to a fresh bowel anastomosis is not allowed.

Control arm

Patients who are not allocated to the treatment group will receive standard treatment, which means no C-Qur™ Film or any other treatment considered to have anti-adhesion properties (for example, corticosteroids, dextran, heparin, icodextrin, *etcetera*) and no placebo will be used.

Outcome measures

The primary outcome measure will be the incidence of adhesions to the primary incision site or the specimen retrieval incision in the case of hand-assisted laparoscopy.

Secondary outcome measures on effectiveness are the extent and severity of adhesions to the primary incision site or specimen retrieval incision, incidence, extent and severity of adhesions at the loop ileostomy or loop/split colostomy site and of adhesions at areas potentially injured during the initial procedure, duration of ileostomy or loop/split colostomy takedown from the start of the takedown to the time the bowel is repositioned in the abdomen, percentage (%) of abdominal wall with adhesions, number of C-Qur™ barrier films used, sizes of C-Qur™ barrier films used, areas treated with C-Qur™ Films (underneath incision, ostomy bowel loops, other areas injured during initial procedure and considered adhesiogenic), reason for not placing film in one or more of the areas considered to be adhesiogenic, incidence of chronic abdominopelvic pain, incidence of other gastrointestinal complaints, quality of life as assessed by Short Form-36 and DASI, and total direct

health care costs (30 days-in-hospital healthcare costs during both hospital stays).

Secondary outcome measures on safety are incidence of postoperative complications. Complications are divided into surgical and medical complications. Surgical complications are superficial incisional surgical site infections, deep incisional surgical site infections, anastomotic leakage, intra-abdominal abscess, peritonitis, unexplained fever, fascia dehiscence, wound dehiscence, postoperative hemorrhage, and postoperative ileus (POI). Medical complications are pulmonary embolism, pneumonia, urinary tract infection, sepsis, and death.

Other secondary outcome measures are reoperations, number of re-laparotomies, number of inserted central venous lines, other re-operations, first postoperative day of oral food intake, parenteral feeding, number of days parenteral feeding required, tube feeding, number of days tube feeding required, first postoperative day of passing flatus, first postoperative day of passing stool, usage of pain medication, daily VAS (Visual Analog Scale) scores, hospital stay, Intensive Care Unit stay, Recovery Unit stay, readmissions within 30 days after discharge, and in-hospital mortality.

Randomization and blinding

Intra-operatively, the treating surgeon judges whether the patient is eligible for definite inclusion. Prior to formation of the temporary loop ileostomy, loop or split colostomy, included patients will be randomized. Patients will be randomized in a 1:1 fashion to the C-Qur™ Film arm (treatment arm) or the control arm. The randomization will be stratified by operative technique (open or hand-assisted laparoscopy). The allocation sequence will be computer-generated through the web-based program Alea©. A researcher who does not participate in the data analysis will manage the randomization process. This way, the researcher who will perform the data analysis is blinded from treatment allocation. Concealment of treatment allocation and blinding of the surgeon performing the index procedure is not possible because the patient will either get the intervention or does not get an intervention at all. Randomization will be noted in the operation reports, allocation will not.

The patient and doctor at the surgical ward who will complete the case report form during the post-operative period is blinded from treatment allocation. To achieve blinding during the data collection of outcome parameters, the surgeon who will perform the ostomy takedown procedure, will not be the same surgeon as the one who performed the index procedure. Because of the absence of clinical notes regarding allocation, however, the initial surgeon is allowed to do the ostomy takedown in case of man-power or organizational problems.

During the postoperative period after the ostomy takedown, the physician at the ward, who will collect the data regarding the post-operative parameters, will be blinded from the treatment allocation of the patient. The patient will stay blinded for the received treatment.

Unblinding protocol

A Data Safety Monitoring Board (DSMB) meeting for safety assessment will be scheduled once every 15 patients have been enrolled. The study will be deblinded when there is a higher mortality rate or incidence of surgical complications than can be expected from data found in the literature. The deblinding will be performed by the same researcher who performs the randomization procedure.

Patients will be informed on request about the performed procedure only after completing the quality-of-life questionnaires 1 year postoperatively.

Data recording and follow-up

All included patients will preoperatively fill in two questionnaires on quality of life (SF-36, short-form 36, and DASI, duke activity status index) and one questionnaire on gastro-intestinal complaints (GIC). Preoperatively, information on the following will be collected: age, sex, weight, height, American Society of Anesthesiologists (ASA) classification, smoking status, Revised Cardiac Risk Index (RCRI), chronic obstructive pulmonary disease (COPD)/asthma, diabetes mellitus, primary clinical diagnosis, medical/surgical history, number of previous laparotomies, type of previous laparotomies, number of previous laparoscopies, type of previous laparoscopies, and medication usage. A physical exam will be performed, which includes vital signs and laboratory collection (to include C-reactive protein (CRP), chemistry, hematology and coagulation) and a pregnancy test if the patient is premenopausal.

Classification of operative wounds based on the degree of microbial contamination, the number of serosal injuries and the number of inadvertent enterotomies will be noted in the source notes and CRF.

The type of abdominal closure (layered or mass fascia closure) and suture material used will be noted in the source notes and CRF.

Patients in both groups will receive the same postoperative treatment. Until patients are discharged, the following parameters will be collected: postoperative complications (superficial incisional surgical site infections, deep incisional surgical site infections, anastomotic leakage, intra-abdominal abscess, peritonitis, unexplained fever, fascia dehiscence, wound dehiscence, postoperative hemorrhage, postoperative ileus (POI), pulmonary embolism, pneumonia, urinary tract infection, sepsis, and death), reoperations, first post-operative day of oral food intake, parenteral feeding, number of days parenteral feeding required, tube feeding, number of days tube feeding required, first post-operative day of passing flatus, first post-operative day of passing stool, usage of medication including pain medication, daily VAS-scores, hospital stay, Intensive Care Unit stay and Recovery Unit stay.

Patients will return 8 to 16 weeks after index surgery to have their ostomy taken down. Clinical follow-up to obtain update(s) on adverse events (AE's), adhesion-related events, changes in concomitant medications, the presence/absence of surgical site infection (SSI) and the type of SSI (if

applicable) will be done during the admission for ileostomy/colostomy takedown. Weight and vital signs will be noted and the following laboratory investigations will be repeated: CRP, sodium (Na), potassium (K), urea, creatinine, hemoglobin, white blood cell count, platelet count, international normalized ratio (INR) and prothrombin time (PT).

Patients in both groups will undergo the same procedure for ostomy closure. To evaluate the adhesions at the loop ileostomy/colostomy site, the incidence, severity and extent of adhesions around the ostomy have to be evaluated during takedown. The time required for takedown of the ostomy is defined as the time from start of the takedown to the time the bowel is repositioned in the abdomen, and this time will be noted on the CRF. The severity of adhesions will be scored according to the Zühlke classification (see Table 2). To assess the extent of adhesions, the ostomy is divided in four quadrants (Figure 2). The extent of adhesions is scored as the number of quadrants containing adhesions (Table 3). After the ileostomy/colostomy takedown is completed, the surgeon will introduce a laparoscope at the ostomy site and evaluate the incidence, extent and severity of adhesions at the incision site and at other areas potentially injured (and covered) during the initial procedure. The severity will be scored according to the Zühlke classification (see Table 2). The extent of adhesions underneath the incision site will be scored through estimation of the area covered by adhesions as a percentage of the total area underneath the incision. The incidence and severity of adhesions at other areas potentially injured during the initial procedure will be scored according to the Zühlke classification (see Table 2).

Figure 2: Quadrants of the ostomy site

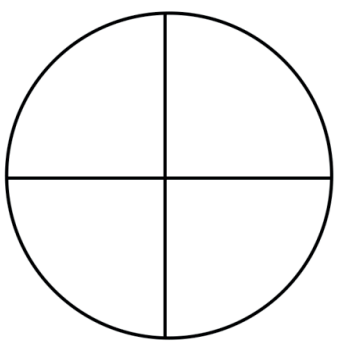

Table 3: Classification to score the extent of adhesions covering the stoma

Score	Observation
0	No adhesions
1	Adhesions present on up to one quadrant of the stoma circle
2	Adhesions present on two quadrants of the stoma circle
3	Adhesions present on three quadrants of the stoma circle
4	Adhesions present on all four quadrants of the stoma circle

One year after randomization, patients in the treatment and control arm will be approached to fill in the same questionnaires on quality of life (SF-36 and DASI) and gastrointestinal complaints (GIC) as preoperatively.

Ethics and informed consent

This study is conducted in concordance with the principles of the Declaration of Helsinki [17] and Good Clinical Practice guidelines. The protocol was ethically approved by the official Independent Review Board Nijmegen (2013/470) and registered nationally (NL45940.091.13).[15] A Data and Safety Monitoring Board (DSMB) is established to perform safety surveillance and to perform interim analysis on the safety data, as described.

Patients will be screened in the outpatient clinic for participation in this study by a surgeon in one of the hospitals that will contribute to this study. Each patient must meet the inclusion/exclusion criteria of this trial. All potentially eligible patients are required to sign an informed consent after careful consideration. Patients have to sign the informed consent prior to the index procedure.

Analysis and sample size

It is hypothesized that the use of the C-Qur™ Film underneath the primary incision reduces the incidence of adhesion at the incision by 30%. This hypothesis is based on the supporting documentation for Seprafilm™ (treatment) versus Control (no treatment) with an adhesion rate of 94% in the control group and 64% in the treatment group.[18-22] We estimate a total drop out of 25% in this study, comprising 10% regular drop out and 15% drop out because of anastomotic leakage. A 15% drop out because of anastomotic leakages is chosen because it is the upper limit of the incidence of this complication. Assuming that the C-Qur™ Film group performs similarly to Seprafilm™, a total of 84 patients, (32 + 10 per group (25% drop out)) would be needed in a randomized study, with 80% power and two-sided alpha = 0.05 in order to detect a 30% reduction in incidence of adhesions.

Statistics

In general, for continuous variables, the mean, standard deviation, median, IQR, minimum and maximum values will be presented. Groups will be compared using the *t*-test or Mann-Whitney *U* test, as appropriate, based on the distribution of the data. For categorical variables, the frequencies and percentage within each category will be calculated. Groups will be compared using the chi-square or Fisher's Exact test, as appropriate, based on the expected counts. All available data will be summarized. Demographics, preoperative, perioperative, and postoperative parameters will be reported and compared for both groups. Descriptive statistics will be presented to describe the trial results. Missing data will be evaluated by the investigators, and appropriate action will be undertaken. In case of skewed baseline data between groups, results will be corrected for this data.

Our primary analysis will focus on the effectiveness and safety of the C-Qur film between the treatment group and the control group. A chi-square or Fisher's Exact test will be performed to assess a significant improvement in the incidence, on the Zühlke score of adhesions underneath the incision site, underneath the loop ileostomy or loop/split colostomy site, and for the extent of adhesions underneath the loop ileostomy or loop/split colostomy site as well. The extent of adhesions underneath the incision site and the time needed for takedown of the ileostomy or loop/split colostomy will be compared using a *t*-test. To assess the safety of the C-Qur film the total incidence of postoperative complications will be compared using a *t*-test or a Mann-Whitney *U* test. The mortality and the incidence for each separate complication will be compared using a chi-square or Fisher's Exact test.

Subgroup analysis will be performed on laparoscopic versus open colorectal resection, and on ileostomy versus colostomy for the incidence, extent and severity of adhesions as described above. Since data collection of the outcome parameters is not blinded when the same surgeon who performed the index procedure also takes down the ostomy, subgroup analysis will be performed for patients with and without blinded data collection of outcome parameters.

Reporting

The CLIPEUS trial findings will be reported in concordance with the Consolidated Standards of Reporting Trials (CONSORT) checklist.[23]

Discussion

Results of this study add to the evidence on the use of anti-adhesive barriers in open and laparoscopic 'hand-assisted' colorectal surgery. Although the ultimate objective of adhesion prevention is to reduce the clinical consequences of adhesions, we chose incidence of adhesions to the incision site as primary outcome measure. Clinical outcomes such as small bowel obstruction,

secondary infertility and adhesiolysis related complications are considered multifactorial and difficult to interpret.[24] Incidence of adhesions at repeat surgery is believed to be the most valuable surrogate endpoint for clinically relevant adhesion prevention, since small bowel obstruction and adhesiolysis at repeat surgery are not likely to occur when complete adhesion reduction in a patient is accomplished. No adhesion under the incision site in particular will benefit patients at re-laparotomy or re-laparoscopy. Recent evidence from our group emphasizes the large disease and socioeconomic burden of adhesions needing lysis at subsequent abdominal surgery.[25]

To be able to evaluate incidence of postoperative adhesions, a second-look surgery model is required, also because noninvasive methods such as cine-magnetic resonance imaging (MRI) have not been validated measuring adhesion reduction.[26] Colorectal resection with temporary loop ostomy is an obvious choice, since colorectal surgery is frequently performed and known for its relatively high incidence of adhesion-related complications.[27] We will include patients undergoing resection for benign or malignant indication. Malignancy is the largest indication for colorectal resection, and since (disease-free) survival has strongly increased, life time risk of adhesion-related complications has increased correspondingly.

In this study, both laparoscopic and open colorectal resections will be included. In many countries, laparoscopic colorectal resection for benign and malignant diseases has gained popularity.[28] Thus, performing only an open colonic resection study would lower the generalizibility of the results on adhesion prevention. Laparoscopic technique is accompanied by less tissue trauma. Hence, it is suggested that laparoscopic colorectal surgery results in fewer adhesions. A recently published population-based register study specifically addressed readmission rate for clinically apparent adhesions after colorectal surgery, comparing the open and laparoscopic approach.[29] Of the total of 187,148 patients included, 11,013 (5.9%) had laparoscopic resection. With a median follow-up of 31.8 months, overall adhesion-related readmission rate was 8.1%; 8.2% after an open approach versus 6.3% after a laparoscopic approach (P <0.001). An important limitation of this study was the higher percentage of emergency operations in the open group compared to the laparoscopic group. The most common underlying disorder for an emergency laparotomy (that is, peritonitis) has a higher adhesion formation propensity. Despite the relative reduction of 23% in the re-admission rate, it should be concluded that clinically relevant consequences of adhesions are substantial also after laparoscopic surgery. A subgroup analysis for open versus laparoscopic resection will be conducted to control for the difference in surgical technique and concomitant adhesion formation.

For the sake of safe and secure placement of the adhesion barrier, only patients undergoing laparoscopic resection with a specimen extraction incision of at least 6 cm will be included in our study. This minimal incisional length was chosen based on previous experience with the C-Qur™ Film. The availability of different sizes of the film and the tissue adherence only at one site improve the

placement in narrow spaces. These characteristics provide potentially better handling when compared to the commonly used HA/CMC barrier film in open colorectal surgery.

Trial status

This trial has been approved by the official Independent Review Board Nijmegen (2013/470).[15] Inclusion has not started.

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9

Summary and general discussion

Summary

A colorectal resection is a common surgical procedure and in the majority of cases performed for colorectal cancer. Either executed by open or laparoscopic approach, trauma to peritoneal surfaces is unavoidable and sometimes extensive. The traumatized tissue often heals with adhesion formation which may have negative clinical consequences. Until recently, postoperative small bowel obstruction was considered the most important complication of adhesions with risk of reoperation, major morbidity and mortality.[1] Recent literature makes clear that difficulty at repeat abdominal surgery is also a major cause of complications due to dissecting adhesions.[2] The studies in this thesis address adhesions in colorectal surgery with focus on consequences of adhesions for quality of cancer resection, adhesiogenic propensity of laparoscopic compared to open colorectal surgery and the potential and expediency to prevent adhesion formation with adhesion barriers in colorectal surgery.

Chapter 1 provides an introduction and outline of this thesis.

Chapter 2 gives an comprehensive overview of the current knowledge regarding inflammatory response of the peritoneum on various pathological triggers, such as surgical trauma, invasive pathogens and tumor. Colorectal cancer surgery is associated with all mentioned triggers. Regardless of the type of injury to the peritoneal mesothelial cells, an inflammatory response is activated attempting to restore the peritoneal surfaces. The peritoneal response comprises four interacting pathways, an immunological, a humoral, a coagulation and a neurogenic pathway. Fibrous tissue connecting organs, surfaces and structures is commonly the ultimate result.

In ***Chapter 3*** the impact of adhesiolysis on clinical and histopathological outcome of colorectal surgery is presented. Despite the fact that colorectal surgery has been the focus of adhesion formation and prevention research in the past decades, the impact of adhesiolysis and associated organ injury on the outcome of colorectal surgery has not been investigated in detail before.

A total of 249 colorectal procedures were selected from an earlier prospective cohort study of adhesiolysis-related problems in elective abdominal surgery.[3] Relevant patient, surgical and medical data were prospectively assessed, before, during and after hospital stay. During colorectal surgical procedures detailed information on adhesions, adhesiolysis and inadvertent organ damage was collected and recorded real-time in a database by an independent researcher present in the operating theatre. Primary outcomes were incidence of adhesions, adhesiolysis time, incidence of bowel defects, seromuscular injury, injury to other organs and structures, and incidence of major surgery related complications (MSRC). Secondary outcomes were other morbidity, oncological outcome, hospital costs, and incidence of hospital readmission within 30 days after discharge.

Adhesions were present in 60.6%, and adhesiolysis was performed in 59.0% of colorectal surgeries. Adhesiolysis resulted in enterotomy in 6% of cases, and in significantly more seromuscular bowel injuries compared to colorectal surgery without necessity to perform adhesiolysis (27% versus 7%). There was no significant difference in other organ injury. Adhesiolysis doubled the incidence of MSRC to 30% and was associated with a higher readmission rate of 15%. There was a trend towards a longer hospital stay and higher costs in the adhesiolysis group. This study was the first to investigate the impact of adhesiolysis on oncological quality of colorectal cancer resection. Data on resection margin and number of lymph nodes harvested were extracted from the pathology reports of the subgroups of 49 patients who underwent a rectal resection and 71 patients who underwent a colon resection for cancer. There were no differences with regard to these histopathological outcomes between patients undergoing colorectal cancer surgery with or without adhesiolysis.

It was concluded that adhesiolysis during colorectal surgery is related to an increased incidence of iatrogenic bowel injuries and MSRC. Despite the technical challenges associated with adhesiolysis, good histopathological results were obtained in oncological resections.

In ***Chapter 4*** the impact of prior abdominal surgery on the outcome of colorectal cancer resection was evaluated. Due to the frequent presence of postoperative adhesions, ranging between 67 and 95% [1,4-6], prior abdominal surgery was thought to increase complexity and morbidity of colorectal cancer surgery. Adhesiolysis is time consuming, associated with a certain percentage of bowel injury and increases postoperative morbidity.[3] Cautious approach to the bowel during adhesiolysis to avoid injury, might compromise access to the operative field and extent of bowel resection, possibly leading to smaller or even incomplete resection margins. A small resection margin has been identified as a risk factor for poor lymph node harvest.[7]

Data on primary colorectal cancer resections between January 2010 and December 2012, registered by all 92 Dutch hospitals performing colorectal cancer surgery, were retrieved from the Dutch Surgical Colorectal Audit (DSCA) prospective database.[8] Primary outcomes were number of lymph nodes harvested, circumferential rectal resection margin (CRM), CRM positivity, and completeness of resection in colon cancer. Besides absolute number of lymph nodes harvested, we used cut-offs of 10 and 12 lymph nodes, based on Dutch and US guidelines.[9,10] Secondary outcomes were postoperative complications and 30-day mortality.

9,042 patients (33.8%) with one or more prior abdominal operations, and 17,679 patients (66.2%) without prior abdominal operations were eligible for inclusion in the analysis. Mean number of lymph nodes was significantly lower in the group with prior abdominal surgery (15.2 versus 15.6 lymph nodes harvested). After prior abdominal surgery 20.7% had less than 10 lymph nodes in the

histopathological specimen compared to 17.8% without prior abdominal surgery (adjusted OR 1.17, 95% CI 1.09 -1.26). No differences were found regarding completeness of resection, mean CRM and CRM positivity, between these groups. There was a small but significant increase in percentage of patients with postoperative complications after prior surgery (OR 1.14; 95% CI 1.07-1.21). Subgroups of different types of abdominal surgery in history as defined in the DSCA database were analyzed regarding number of lymph nodes, the cut-offs 10 and 12 lymph nodes, incomplete resection and CRM. No effect on histopathological results was shown for prior upper gastrointestinal and urogenital surgery. Prior colorectal surgery was associated with a significantly decreased number of lymph nodes in colon specimens, and a significant increase of patients with CRM positivity of rectal specimens. Prior hepatobiliary surgery and prior other abdominal surgery were associated with more patients having a colonic resection specimen with less than 10 lymph nodes. Prior hepatobiliary surgery was also associated with an increased percentage of patients with less than 12 lymph nodes in their rectal resection specimen. The negative effect of prior abdominal surgery on histopathological outcome and postoperative morbidity found in this study is small. It is likely that more invasive and extensive prior surgery has a higher degree of impact on colorectal cancer resection. Unfortunately, data on approach and extent of prior surgery, and number of prior operations, were not available in the DSCA database.

We concluded from this study that abdominal surgery compromises the quality of resection and increases postoperative morbidity in patients with primary colorectal cancer.

It is a general assumption that minimally invasive surgery is associated with less adhesion formation.[11] Adhesion incidences after open and laparoscopic colorectal surgery were evaluated in ***Chapter 5***. In a prospective, observational, multicenter study, the incidence and impact of adhesions were compared between patients who underwent liver surgery for colorectal metastases after prior open and after prior laparoscopic colorectal cancer resection. Primary outcome was the incidence of adhesions to the ventral abdominal wall around the incision(s) made for the previous colorectal cancer resection. Secondary outcomes were total incidence of adhesions, extent and Zühlke classification of adhesions, performance of adhesiolysis, duration of adhesiolysis, surgical complications, serious adverse events, length of stay, and episodes of bowel obstruction in the interval between colorectal and liver surgery.

A total of 90 (59.6%) patients with previous open and 61 (40.4%) patients with previous laparoscopic colorectal cancer resection were compared. Mean time interval between surgeries was significantly longer in the open group compared to the laparoscopic group. In the open group adhesions to the ventral abdominal wall around the primary incision were present in 78.9% of patients, compared to 37.7% in the laparoscopic group (P<0.001). Incidence of adhesions to the complete ventral

abdominal wall and overall incidence of any adhesions were also significantly higher after open surgery. Still, incidence of overall adhesions was 62.3% after laparoscopic colorectal resection, and incidence of visceral adhesions was not significantly different between the open and laparoscopic group.

This large prospective study is the first to provide complete and clinically relevant information on adhesion formation after colorectal cancer surgery by laparoscopic approach. The findings challenge the broad opinion that laparoscopy minimizes adhesion formation, and might also be a basis to use adhesion barriers in laparoscopic colorectal surgery.

In ***Chapter 6*** a systematic review and meta-analysis is presented evaluating the evidence of benefits and harms of four commercially available adhesion barriers. All randomised clinical trials assessing use of oxidised regenerated cellulose, hyaluronate carboxymethylcellulose, icodextrin, or polyethylene glycol in abdominal surgery were collected. The use of a barrier was compared with no barrier for nine predefined outcomes, graded for clinical relevance. Reoperation for adhesive small bowel obstruction was the primary outcome. Secondary outcomes were serious adverse events, total incidence of adhesions, reoperation time, small bowel obstruction from any cause, site-specific incidence of adhesions, and adhesion score. We assessed systematic error, random error, and design error with the error matrix approach.

The risks of systematic and random errors were low. No trials reported data for the effect of oxidized regenerated cellulose or polyethylene glycol on reoperations for adhesive small bowel obstruction. Some evidence suggests that hyaluronate carboxymethylcellulose reduces the incidence of reoperations for adhesive small bowel obstruction (RR 0.49, 95% CI 0.28–0.88). For icodextrin, reoperation for adhesive small bowel obstruction did not differ significantly between groups (RR 0.33, 95% CI 0.03–3.11). No barriers were associated with an increase in serious adverse events. Oxidised regenerated cellulose reduced the incidence of adhesions (relative risk [RR] 0.51, 95% CI 0.31–0.86).

We concluded that oxidized regenerated cellulose and hyaluronate carboxymethylcellulose can safely reduce clinically relevant consequences of adhesions.

Doubts about cost-effectiveness and the need for adhesion prevention in the minimally invasive era probably underlie the current clinical practice to rarely use adhesion barriers.[11] In ***Chapter 7*** a decision tree model is presented for the use of an adhesion barrier in open and laparoscopic colorectal surgery.

Current clinical practice (no adhesion barrier) [11] is compared with the use of an adhesion barrier. The clinical consequences of adhesions considered in the model are adhesive small bowel obstruction

(ASBO) and difficulties at repeat abdominal surgery. The best available evidence from the literature and hospital data are used for the probabilities and costs in the model. Hyaluronate carboxymethylcellulose (HA/CMC) is the only adhesion barrier with consistent evidence available on adhesion prevention and prevention of clinical consequences of adhesions in visceral surgery. Although the evidence for HA/CMC does not include laparoscopic surgery, we extrapolated the efficacy data of HA/CMC in open colorectal resection to the laparoscopic model. Outcomes of the model are effect on incidence of ASBO and incidence of adhesions at repeat abdominal surgery, direct healthcare costs, and incremental cost effectiveness ratio of adhesion barrier for one patient with adhesions prevented.

Taking the parameters at their baseline values for the open cohort, the adhesion barrier strategy was both cheaper and more effective than the no adhesion barrier strategy. In the laparoscopic cohort the adhesion barrier strategy was also more effective, but $40 more expensive per patient treated taking a four years follow-up period into account. Incremental cost effectiveness ratio was $135 per patient with adhesions prevented in the laparoscopic colorectal surgery group. Probabilistic sensitivity analysis showed that the use of an adhesion barrier had a 65% probability of being cost-reducing in the open cohort, this probability was 37% in the laparoscopic cohort. Threshold analysis in the open cohort showed that with costs for the barrier of $732 or more, the use of an adhesion barrier would no longer be cost-reducing. The same effect was seen with the reoperation rate set to 15% or less. In the laparoscopic cohort the thresholds for cost-reduction with an adhesion barrier were costs for the adhesion barrier of $589, and a repeat surgery rate of 25%. Worst and best case scenario for efficacy of the adhesion barrier were performed by means of analysis with the upper and lower limits of the confidence intervals. Worst case scenario resulted in an incremental cost effectiveness ratio for one patient with adhesions prevented of $908 in the open and $1,663 in the laparoscopic cohort. Best case scenario resulted in applying an adhesion barrier in both open and laparoscopic colorectal surgery being cost-reducing.

Adhesions, adhesive small bowel obstruction and adhesion-related problems at repeat abdominal surgery can effectively be reduced with the use of an adhesion barrier, in both open and laparoscopic colorectal surgery. For laparoscopic colorectal surgery this might be accompanied by limited costs, and for colorectal surgery this would probably result in cost savings.

In ***Chapter 8*** we present the study protocol for a randomized controlled trial on the efficacy and safety of a novel adhesion barrier membrane, C-Qur^{TM} film, in patients undergoing open or hand-assisted laparoscopic colorectal resection. The film is available in different sizes and only tissue adherent at one side, making it potentially more suitable for placement in narrow spaces compared to other barriers. The primary outcome measure is incidence of adhesions to the incision site.

Incidence of adhesions is believed to be the most valuable surrogate endpoint for clinically relevant adhesion prevention, since small bowel obstruction and adhesiolysis at repeat surgery are not likely to occur when complete adhesion prevention is accomplished. The results of this study will give valuable information on adhesion formation after laparoscopic compared to open colorectal cancer resection, and the effectiveness of the use of an adhesion barrier to prevent adhesion formation.

General discussion

Adhesions complicating colorectal surgery

This thesis addresses adhesions as complicating factor during colorectal surgery with two different approaches. In chapter 3 the analysis of all cases of colorectal surgery from an earlier prospective cohort study of adhesiolysis-related problems in elective abdominal surgery is presented. Adhesiolysis during colorectal surgery resulted in bowel injury, doubling of postoperative surgical complications, and a higher readmission rate. In chapter 4 analysis of a large nationwide prospective database of colorectal cancer resections showed that previous abdominal surgery was also associated with an increase of postoperative morbidity. This negative impact of previous abdominal surgery is most likely attributable to postoperative adhesion formation, since all types of abdominal surgery have a substantial risk of postoperative adhesion formation.[1,4-6] The strength of the prospective cohort study lies within the completeness of detailed information, in particular on adhesions and adhesiolysis, complications, and costs. However, since the cohort was relatively small and from a single Dutch university medical center, results cannot be generalized for other hospitals or other countries. Moreover, subgroup analysis to identify specific risk factors was not possible due to the small number of patients. Main advantage of the nationwide database study is the external validity and results can be applied to all patients undergoing primary colorectal cancer resection in the Netherlands.[12] However, a database study harbors the risk of retrospective, and potentially incorrect and/or incomplete data. Despite the magnitude of the group of patients, possibilities for subgroup analysis were limited because not all relevant variables were registered in the database. As a result, the difference between the two studies in complication rate cannot be investigated and explained in detail. Most likely the surgical history of the patients included in the prospective cohort study is more extensive than of the patients in the national database, and registration of the complications in the prospective study might be more complete. The conclusion from both studies that adhesions worsen the early outcome of colorectal surgery, gains strength because it is supported by two different study methods. Future research on patient-reported outcomes (PROs), such as symptoms, quality of life and functional status, could underline the negative impact of adhesions from a patient's perspective. In abdominal surgery quality of care is traditionally measured by mortality and morbidity, and seldom by PROs. Knowing the impact of adhesions on PROs after colorectal surgery would aid in shared decision making, especially in elective repeat surgery for benign diseases and for colorectal cancer surgery in the elderly.

The known difficulties caused by adhesions during repeat abdominal surgery led to the hypothesis that adhesions could negatively impact oncological quality of resection in colorectal cancer surgery.[2,3] We were the first investigating this potential correlation, and performed this study in the

aforementioned prospective cohort with complete and detailed information, and in a large nationwide database. The pathology reports of all cases of colorectal cancer resection from the prospective cohort study were retrospectively analyzed. The reliability of the pathology reports was considered high, since standardized reports for colorectal cancer are used as recommended by the National Guidelines for Colorectal Cancer Surgery, following the Dataset for colorectal cancer (2nd edition) of the Royal College of Pathologists.[13,14] The cohort only comprised 120 patients with colorectal cancer resection and there were even smaller numbers of patients in subgroup analyses which hampered making definite conclusions. Again, generalizability of the results may be an issue since the cohort was from one center, and local standards of resection might have influenced histopathological outcomes. However, rates of patients with less than 10 lymph nodes harvested for both colon (18.6%) and rectal (26.5%) cancer were comparable with the rates in the Dutch Surgical Colorectal Cancer Audit (16% and 32% respectively in 2011).[8] The hypothesis that prior abdominal surgery, as surrogate parameter for adhesions, is associated with worse oncological quality of colorectal resection was confirmed in the database study. The small but significant differences can be attributed to the very large number of patients and raises the question whether this difference is clinically relevant. 20.7% of patients with prior abdominal surgery compared to 17.8% of patients without prior abdominal surgery with less than 10 lymph nodes harvested seems a small difference. However, a one-sixth increase of patients exposed to adjuvant systemic therapy or a likely increase in patients with local or regional recurrence, should not be ignored. Previous studies have shown that an inadequate number of lymph nodes evaluated is associated with impaired outcome [15,16] and CRM positivity increases local recurrence risk.[17] The lack of data on adhesions and performance of adhesiolysis in this database does not permit definitive conclusions on the role of adhesions. Since data on prior abdominal operations in the database was limited to a nonspecific anatomical classification, it was not possible to create specific subgroups of patients, i.e. open versus laparoscopic, or according to severity and extent of prior abdominal surgery. It is likely that more invasive and extensive prior surgery will have a higher degree of impact on future colorectal cancer resection.[3] Apart from a worse oncological quality of colorectal resection, the higher rate of postoperative complications in patients with prior abdominal surgery may worsen long-term oncological outcome. A patient with prior abdominal surgery has a higher likelihood of developing postoperative complications risking a later start of adjuvant chemotherapy or no start at all.[18] It is usually accepted that adjuvant chemotherapy should begin within 8 weeks after surgery, and initiation beyond 3 months after surgery is associated with an increase in cancer specific mortality.[19,20] Awareness of these negative effects should stimulate surgeons when performing an oncological resection in patients with an abdominal surgery in history, to dissect the right planes and obtain sufficient amounts of lymph nodes, also in the presence of adhesions. It would be even better

to prevent the formation of adhesions by using appropriate adhesion barriers from the beginning at the first abdominal surgery.

Adhesions as a result of open or laparoscopic colorectal surgery

Reported incidences of adhesions after abdominal surgery are based on old studies of open abdominal surgery.[5,6] Colorectal surgery in particular has consistently been associated with high rates of adhesion formation and adhesion related complications.[1,2] With introduction of laparoscopic surgery and reports of reduced inflammatory response associated with this minimally invasive technique it is generally assumed that adhesion formation is minimal and related complications are substantially reduced.[11,21] However, data on adhesions after laparoscopic colorectal surgery supporting this assumption, are scarce and of limited quality. For instance, the claim that laparoscopy largely solves the problem of adhesions by reported better fertility rates or less adhesions after laparoscopic restorative proctocolectomy, is solely based on adhesion assessment limited to specific anatomical sites, and involves selection and publication bias.[22,23] In this thesis, adhesions after open and laparoscopic colorectal cancer surgery are addressed in a prospective multicenter study, and in a decision analytic model. In the first study, adhesion formation is compared after previous laparoscopic or open resection of colorectal cancer. The chosen population of patients in whom liver surgery was performed for metastases, enabled second look surgery to reliably assess both abdominal wall and visceral adhesions. Strong aspect of the study is the multicenter approach. The study showed that laparoscopy reduces adhesion formation, mainly to the parietal peritoneum. Incidence of adhesions, in particular between viscera, was still more than 60%. These findings are of particular importance for repeat surgery. Patients undergoing laparoscopy will benefit from a lower incidence of abdominal wall adhesions, which facilitates re-entry and lowers risk of organ injury by trocar introduction. The benefit of laparoscopy on clinically relevant endpoints is addressed in a decision analytic model. The best available evidence on adhesion formation, adhesive small bowel obstruction (ASBO) and adhesions complicating repeat surgery was synthesized, to evaluate the adhesion related outcome and health care costs after open and laparoscopic colorectal surgery. The probability of ASBO was 6.6% after laparoscopic colorectal surgery, a 24% reduction relative to 8.6% ASBO after open colorectal surgery. This reduction corresponds with a large population-based epidemiological study and a recent meta-analysis, reporting a 24% (6.3% versus 8.2% in 2.5 years) reduction of adhesion-related readmissions and a 25% (3% versus 4%) reduction of small bowel obstruction in favor of laparoscopic compared to open colorectal surgery.[24,25] Remarkably, the reduction in ASBO and adhesion-related readmissions is less than the 30% reduction in adhesion incidence demonstrated in our prospective, multicenter study. The studies collectively

reject the assumption that adhesions would no longer be an issue in the laparoscopic era. Unfortunately, patients remain at risk for developing small bowel obstruction, or requiring adhesiolysis at repeat surgery with associated complications.

Adhesion barriers

The mainstays of adhesion prevention are minimization of surgical trauma and adhesion barriers. Adhesion barriers are seldom used due to perceived high costs, doubts about the effectiveness on clinically relevant outcomes, and doubts about the need for adhesion prevention in the laparoscopic era.[11] Laparoscopy reduces surgical trauma, but the reduction of adhesions associated with a laparoscopic approach is limited, as apparent from this thesis. Adhesion prevention in laparoscopy raises an issue with existing adhesion barriers. Adhesion barrier membranes, with proven efficacy in open colorectal surgery, are difficult to apply in laparoscopic surgery, and there are no consistent efficacy data available for this application.[26.27] Liquid or gel barriers are more appropriate for laparoscopic use, but in the systematic review and meta-analysis no evidence for laparoscopic colorectal surgery was shown. Regarding other surgical specialties, there is some evidence on use of liquid or gel barriers. The liquid barrier icodextrin 4% was not proven effective in reducing de novo adhesions in laparoscopic gynecological surgery, and efficacy of sprayable HA/CMC in laparoscopic radical prostatectomy was determined with a weak primary endpoint.[28,29] Even if efficacy in other specialties was proven, this cannot be extrapolated to colorectal surgery, due to large differences in factors that may affect adhesion formation e.g. bacterial contamination, large peritoneal surfaces. Altogether we plea for renewed initiatives to develop and study sprays, gels and other soluble agents as adhesion barriers in laparoscopic colorectal surgery.[30]

In a decision tree model for open and laparoscopic colorectal surgery, the efficacy of HA/CMC film in open colorectal surgery was extrapolated to the laparoscopic cohort. The balance between the costs of the adhesion barrier, and the potential cost reduction that can be achieved by prevention of adhesions and adhesion-related complications, was inventoried. The model showed that adhesive small bowel obstruction and adhesion-related problems at repeat abdominal surgery are reduced with cost savings in open surgery and limited costs in laparoscopic surgery. Combined with the 62% incidence of adhesions and limited reduction in adhesion related complications after laparoscopy, these findings warrant effective methods of adhesion prevention in laparoscopy. There are no ongoing trials on adhesion barriers in laparoscopic colorectal surgery identified in the available trial registries. In chapter 8 of this thesis the study protocol for a novel adhesion barrier film in open and hand-assisted laparoscopic colorectal surgery is presented. Advantage of this barrier is that a similar

efficacy compared to other barrier films is expected, but its design would offer good handling characteristics for placement through small incisions in laparoscopic colorectal surgery. Limitation of the study design is that visceral adhesions will not be optimally prevented, since the protocol only demands barrier placement underneath the incision, and it is optional at other areas considered to be adhesiogenic . Moreover, the progress of the study is hampered because it is unclear whether the production of the barrier will be continued. The ambiguity in this study, and the lack of current trials on adhesion barriers in laparoscopic colorectal surgery, underlines that there is reluctance to invest in development of adhesion barriers. The limited belief in adhesion barriers among surgeons seems a key factor for this reluctance.[11] Difficulties encountered in adhesion prevention studies, such as need for second look surgery, need for long term follow up and large numbers of patients for clinically relevant endpoints, are possible other objections.[31] Assessment of visceral slide with dynamic magnetic resonance imaging might eliminate the need for second look surgery, but needs further validation.[32]

Breakthrough measure combating the burden of postoperative adhesions is to increase awareness of the problem and solutions to the problem among other stakeholders than doctors. Actions should be undertaken to inform patients who will undergo colorectal surgery about their long term risk. Insurance companies should be well aware of the long term benefits of adhesion prevention at initial surgery and increase incentive to routinely use adhesion barriers in colorectal surgery. Funding bodies and companies should recognize postoperative adhesion formation as a important health-economic problem and fund research in this area. Preventing adhesion formation from initial abdominal surgery is the critical step in breaking the sequence of per- and postoperative complications caused by adhesions and a subsequent life-long risk of adhesion-related problems.

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Nederlandse samenvatting

Samenvatting

Colorectale resecties worden veelvuldig verricht. De meest voorkomende indicatie voor een resectie is een colorectaal carcinoom. De chirurgische procedure kan door middel van een open of laparoscopische benadering worden uitgevoerd. Bij beide benaderingen is schade aan peritoneale oppervlakken onvermijdelijk en soms zelfs zeer uitgebreid. Genezing van het beschadigde weefsel gaat vaak gepaard met adhesievorming, wat negatieve klinische gevolgen kan hebben. Tot voor kort werd postoperatieve dunne darmobstructie, met risico op heroperatie, hoge morbiditeit en mortaliteit beschouwd als de belangrijkste complicatie van adhesies. Inmiddels zijn er publicaties verschenen waarin juist complicaties tengevolge van adhesiolyse bij abdominale reoperaties genoemd worden als meest ernstige gevolg van postoperatieve adhesies. De studies in dit proefschrift gaan over adhesies in relatie tot colorectale chirurgie. We hebben onderzoek gedaan naar de invloed van adhesies op de kwaliteit van resectie van colorectaal carcinoom, naar adhesievorming veroorzaakt door laparoscopische vergeleken met open colorectale chirurgie, en naar de mogelijkheid en effectiviteit van het voorkomen van adhesievorming met behulp van adhesie 'barriers'.

Hoofdstuk 1 geeft een inleiding en schetst de hoofdlijnen van dit proefschrift.

Hoofdstuk 2 geeft een uitgebreid overzicht van de huidige kennis over de reactie van het peritoneum op verschillende pathologische prikkels, zoals chirurgisch trauma, invasieve ziekteverwekkers en tumor. Al deze prikkels kunnen voorkomen bij een (resectie van) colorectaal carcinoom. Ongeacht het type schade aan de peritoneale mesotheelcellen ontstaat er een ontstekingsreactie als eerste begin om de peritoneale oppervlakken weer te herstellen. De peritoneale reactie omvat vier geïntegreerde processen: een immunologische, een humorale, een stollings- en een neurogene route. Vaak is het uiteindelijke resultaat dat er bindweefsel ontstaat dat oppervlakken van verschillende organen en structuren verbindt.

In ***hoofdstuk 3*** wordt de impact van adhesiolyse op de klinische en de histopathologische uitkomst van colorectale chirurgie uiteen gezet. In totaal 249 colorectale procedures werden geselecteerd uit een eerdere prospectieve cohortstudie over adhesiolyse gerelateerde problemen in electieve abdominale chirurgie. Relevante patiënteigenschappen, chirurgische en medische gegevens werden prospectief verzameld voor, tijdens en na het verblijf in het ziekenhuis. Tijdens colorectale chirurgische ingrepen werd gedetailleerde informatie over adhesies, adhesiolyse en onbedoelde orgaanschade in een databank geregistreerd door een onafhankelijk onderzoeker die aanwezig was in de operatiekamer. De primaire uitkomsten waren incidentie van de adhesies, de adhesiolyseduur, de incidentie van darmletsels, seromusculair letsel, schade aan andere organen en structuren en de incidentie van ernstige, aan de operatie gerelateerde, complicaties. Secundaire uitkomsten waren

overige morbiditeit, oncologische uitkomst, ziekenhuiskosten en de incidentie van heropname in het ziekenhuis binnen 30 dagen na ontslag.

Adhesies waren aanwezig in 60,6% van de gevallen en adhesiolyse werd uitgevoerd in 59,0% van de colorectale operaties. Adhesiolyse leidde in 6% van de gevallen tot een enterotomie, en tot significant meer seromusculair darmletsel vergeleken met colorectale chirurgie zonder noodzaak tot adhesiolyse (27% versus 7%). Er was geen significant verschil in andere orgaanschade. Adhesiolyse verdubbelde de incidentie van ernstige, aan de operatie gerelateerde, complicaties tot 30% en was geassocieerd met een hogere incidentie van heropnames (15%). Er was een trend naar een langere opnameduur en hogere kosten in de adhesiolysegroep. Deze studie was de eerste waarin het effect van adhesiolyse op oncologische kwaliteit van resectie van colorectaal carcinoom is onderzocht. Gegevens over resectiemarge en aantal geoogste lymfklieren werden verkregen uit de pathologieverslagen van de subgroepen van 49 patiënten die een rectumresectie en 71 patiënten die een colonresectie voor kanker ondergingen. Deze histopathologische resultaten bleken niet verschillend tussen patiënten die een resectie met of zonder adhesiolyse ondergingen.

De conclusie is dat adhesiolyse tijdens colorectale chirurgie samenhangt met een verhoogde incidentie van iatrogene darmletsels en ernstige, aan de operatie gerelateerde, complicaties. Ondanks de technische uitdagingen waarmee adhesiolyse gepaard kan gaan, werden goede histopathologische resultaten verkregen bij oncologische resecties.

In ***hoofdstuk 4*** wordt de invloed van eerdere abdominale chirurgie op het resultaat van een resectie voor een colorectaal carcinoom geëvalueerd. Omdat postoperatieve adhesies veelvuldig voorkomen, variërend tussen 67 en 95%, werd gedacht dat eerdere abdominale chirurgie de complexiteit en morbiditeit van een operatie voor colorectaal carcinoom verhogen. Adhesiolyse is tijdrovend en wordt geassocieerd met darmletsels en verhoogde postoperatieve morbiditeit. Een voorzichtige benadering van de darm tijdens adhesiolyse om letsel te voorkomen kan ertoe leiden dat de chirurg een beperktere toegang tot het operatiegebied heeft en de omvang van de darmresectie beperkt. Dit leidt mogelijk tot kleinere of zelfs onvolledige resectiemarges. Een kleine resectiemarge is een risicofactor voor een inadequaat aantal lymfeklieren in het preparaat.

Gegevens van primaire resecties van colorectaal carcinoom tussen januari 2010 en december 2012, geregistreerd door alle 92 Nederlandse ziekenhuizen waar deze operaties werden uitgevoerd, werden verkregen uit de Dutch Surgical Colorectal Audit (DSCA) prospectieve database. Primaire uitkomsten waren het aantal geoogste lymfeklieren, de rectale circumferentiële resectie marge (CRM), CRM positiviteit, en radicaliteit van resectie van het coloncarcinoom. Naast het absolute aantal geoogste lymfeklieren, gebruikten we afkapwaarden van 10 en 12 lymfeklieren, gebaseerd op de Nederlandse en Amerikaanse richtlijnen. Secundaire uitkomsten waren postoperatieve complicaties en mortaliteit binnen 30 dagen.

9042 patiënten (33,8%) met één of meer eerdere abdominale operaties, en 17.679 patiënten (66,2%) zonder voorafgaande abdominale chirurgie kwamen in aanmerking voor inclusie in de analyse. In de groep met eerdere abdominale chirurgie was het gemiddelde aantal lymfeklieren significant lager (15,2 versus 15,6 lymfeklieren). Na eerdere abdominale chirurgie had 20,7% minder dan 10 lymfeklieren in het histopathologische preparaat ten opzichte van 17,8% zonder eerdere buikoperaties (aangepaste OR 1,17, 95% CI 1,09 -1,26). Er werden geen verschillen gevonden met betrekking tot de radicaliteit van resectie, gemiddelde CRM en CRM positiviteit tussen deze groepen. Er was een kleine maar significante stijging van het percentage patiënten met postoperatieve complicaties na eerdere abdominale chirurgie (OR 1.14; 95% CI 1,07-1,21).

Het aantal lymfeklieren, de afkapwaarden 10 en 12 lymfeklieren, de radicaliteit van de resectie en de CRM werden geanalyseerd voor subgroepen met een bepaald type/locatie van de abdominale chirurgie in de voorgeschiedenis, zoals gedefinieerd in de DSCA-databank. Eerdere chirurgie van de bovenste tractus digestivus en eerdere urogenitale chirurgie bleken geen effect te hebben op de histopathologische resultaten. Eerdere colorectale chirurgie hing samen met een significant verminderd aantal verwijderde lymfeklieren bij resecties voor coloncarcinoom, en een significante toename van patiënten met een positieve CRM bij resecties voor het rectum carcinoom. Patiënten met een eerdere hepatobiliaire operatie en eerdere overige buikoperaties hadden vaker minder dan 10 lymfklieren in het colon resectiepreparaat. En eerdere hepatobiliaire operatie was ook geassocieerd met een verhoogd percentage patiënten dat minder dan 12 lymfeklieren in het rectum resectiepreparaat had. Er bestond een klein negatief effect van eerdere buikoperaties op de histopathologische resultaten en postoperatieve morbiditeit. Waarschijnlijk is het effect op de resectie van colorectaal carcinoom groter afhankelijk van hoe invasief en uitgebreid de eerdere chirurgie is geweest. Helaas waren in de DSCA-databank geen gegevens beschikbaar over de gekozen benadering en omvang van eerdere operaties, noch over het aantal eerdere operaties.

We concluderen uit deze studie dat bij patiënten die een primaire resectie van colorectaal carcinoom ondergaan eerdere buikoperaties de oncologische kwaliteit van resectie bedreigen en de postoperatieve morbiditeit verhogen.

In het algemeen wordt aangenomen dat minimaal invasieve chirurgie samenhangt met minder adhesieformatie. De incidentie van adhesies na open en laparoscopische colorectale chirurgie werd geëvalueerd in ***hoofdstuk 5***. In een prospectieve, observationele, multicenterstudie werden bij patiënten die een leveroperatie voor colorectale metastasen ondergingen de incidentie en impact van adhesies vergeleken tussen patiënten die voorafgaand een open of een laparoscopische colorectale resectie hadden ondergaan. De primaire uitkomstmaat was de incidentie van adhesies aan de ventrale buikwand rond de incisie gemaakt voor de eerdere colorectale resectie. Secundaire uitkomsten waren totale incidentie van adhesies, omvang en Zühlke-classificatie van adhesies, het

verrichten van adhesiolyse, duur van adhesiolyse, chirurgische complicaties, ernstige complicaties, opnameduur en episodes van darmobstructie in de periode tussen colorectale resectie en leverchirurgie.

Een totaal van 90 (59,6%) patiënten met eerdere open en 61 (40,4%) patiënten met eerdere laparoscopische resectie van colorectale kanker werden vergeleken. Het gemiddelde tijdsinterval tussen de twee operaties was significant groter in de open groep vergeleken met de laparoscopische groep. In de open groep waren adhesies aan de ventrale buikwand rond de primaire incisie aanwezig in 78,9% van de patiënten, vergeleken met 37,7% in de laparoscopische groep (P <0,001). De incidentie van adhesies ergens anders aan de ventrale buikwand en de totale incidentie van adhesies (buikwand en/of visceraal) waren ook significant hoger na een open operatie. Echter, nog steeds was totale incidentie van adhesies (buikwand en/of visceraal) hoog met 62,3% na een laparoscopische colorectale resectie, en de incidentie van viscerale adhesies was niet significant verschillend tussen de open en laparoscopische groep.

Deze grote prospectieve studie is de eerste met volledige en klinisch relevante gegevens over adhesies na laparoscopische resectie van colorectaal carcinoom. De bevindingen bevestigen eerdere studies dat laparoscopie minder adhesies geeft, maar weerleggen de algemeen heersende mening dat laparoscopie adhesieformatie minimaliseert. Deze bevindingen kunnen de wetenschappelijke basis vormen om ook bij laparoscopische colorectale chirurgie adhesiebarriers te gebruiken.

In ***hoofdstuk 6*** wordt een systematische review en meta-analyse gepresenteerd van het bewijs voor de effectiviteit en veiligheid van de vier commercieel verkrijgbare adhesiebarriers. Alle gerandomiseerde klinische trials die het gebruik van 'oxidized regenerated cellulose', 'hyaluronate carboxymethylcellulose', 'icodextrin', of 'polyethylene glycol' in abdominale chirurgie evalueerden, werden verzameld. Het gebruik van een barrier werd vergeleken met geen barrier op negen vooraf bepaalde eindpunten, geclassificeerd naar klinische relevantie. Heroperatie voor adhesiegerelateerde dunne darmobstructie was de primaire uitkomstmaat. Secundaire uitkomsten waren ernstige complicaties, de totale incidentie van adhesies, heroperatie tijd, dunne darmobstructie ongeacht de oorzaak, locatie-specifieke incidentie van adhesies, en de adhesiescore. We beoordeelden systematische fouten, toevallige fouten en ontwerpfouten door middel van een nieuwe 'error-matrix'-aanpak.

De risico's van systematische en toevallige fouten waren laag. Er waren geen studies naar het effect van oxidized regenerated cellulose of polyethylene glycol op reoperaties voor adhesiegerelateerde dunne darmobstructie. Er zijn aanwijzingen dat hyaluronate carboxymethylcellulose de incidentie van reoperaties voor adhesiegerelateerde dunne darmobstructie vermindert (RR 0,49, 95% CI 0,28-0,88). Voor icodextrin was er geen significant verschil in reoperatie voor adhesiegerelateerde dunne darmobstructie (RR 0,33, 95% CI 0,03-3,11). Het gebruik van geen van de barriers was geassocieerd

met een toename van ernstige complicaties. Het gebruik van oxidized regenerated cellulose verlaagde de incidentie van adhesies (relatief risico [RR] 0.51, 95% CI 0,31-0,86).

We concluderen dat is bewezen dat oxidized regenerated cellulose en hyaluronate carboxymethylcellulose op een veilige manier het risico op klinisch relevante gevolgen van adhesies verminderen.

In de huidige klinische praktijk worden adhesiebarriers zelden gebruikt. Twijfels over kosteneffectiviteit en de noodzaak van adhesiepreventie in het minimaal invasieve tijdperk liggen hieraan mogelijk aan ten grondslag. In ***hoofdstuk 7*** wordt een beslisboommodel gepresenteerd voor het gebruik van een adhesiebarrier in open en laparoscopische colorectale chirurgie.

De huidige klinische praktijk (geen adhesie barrier) werd vergeleken met gebruik van een adhesiebarrier. De klinische gevolgen van adhesies die in het model werden meegenomen zijn adhesiegerelateerde dunne darmobstructie (ASBO) en moeilijkheden bij abdominale reoperatie. Het best beschikbare bewijs uit de literatuur en ziekenhuis gegevens werden gebruikt voor de kansen en de kosten in het model. Hyaluronate carboxymethylcellulose (HA/CMC) is de enige adhesiebarrier waarvan consistente gegevens beschikbaar zijn ten aanzien van adhesiepreventie en preventie van klinische gevolgen van adhesies in viscerale chirurgie. Bij gebrek aan bewijs voor HA/CMC in laparoscopische chirurgie, werden de werkzaamheid van de HA/CMC in de open colorectale resectie geëxtrapoleerd naar het laparoscopische model. Uitkomsten van het model waren het effect op de incidentie van ASBO en de incidentie van adhesies bij abdominale reoperaties, de directe kosten van de gezondheidszorg, en 'incremental cost effectiveness'-ratio van de adhesiebarrier voor het voorkomen van adhesies bij één patiënt.

Uitgaande van de 'baseline'-waarden van de parameters en een vier jaar follow-upperiode was de adhesiebarrierstrategie voor het open cohort zowel goedkoper als effectiever dan geen adhesiebarrierstrategie. In het laparoscopische cohort was de adhesiebarrierstrategie ook effectiever, maar waren de kosten $ 40 hoger per behandelde patiënt. De incremental cost effectiveness-ratio was $ 135 per patiënt waarbij adhesies voorkomen werden in de laparoscopische colorectale chirurgie-groep. Probabilistische sensitiviteitsanalyse toonde een 65% waarschijnlijkheid van kostenvermindering met gebruik van een adhesiebarrier in het open cohort. Die kans was 37% in het laparoscopische cohort. Een analyse van de drempelwaarden toonde aan dat in het open cohort het gebruik van een adhesiebarrier niet langer kostenreducerend was als de prijs voor de barrier $ 732 of meer was, of als er een kans op reoperatie van 15% of minder was. In het laparoscopische cohort waren de drempels voor kostenreductie met een adhesiebarrier een barrier van $ 589 of minder, en een reoperatiekans van 25% of meer. We hebben een slechtste en beste scenario voor de effectiviteit van de adhesiebarrier uitgevoerd door middel van een analyse met de boven- en ondergrenzen van de betrouwbaarheidsintervallen. Het slechtste scenario resulteerde in een

incremental cost effectiveness-ratio per patiënt met uitblijven van adhesies van $ 908 in het open en $ 1663 in het laparoscopische cohort. In het beste scenario was gebruik van een adhesiebarrier kostenreducerend in zowel open als laparoscopische colorectale chirurgie.

De conclusie is dat adhesies, adhesiegerelateerde dunne darmobstructie en adhesiegerelateerde problemen bij abdominale reoperatie effectief gereduceerd kunnen worden met behulp van een adhesiebarrier, in open en laparoscopische colorectale chirurgie. Voor laparoscopische colorectale chirurgie kan dit gepaard gaan met beperkte kosten en voor open colorectale chirurgie zal dit waarschijnlijk leiden tot kostenbesparing.

In ***hoofdstuk 8*** presenteren we het protocol voor een gerandomiseerd gecontroleerd onderzoek over de werkzaamheid en veiligheid van een nieuwe adhesiebarriermembraan, C-Qur^{TM} film, bij patiënten die een open of hand-assisted laparoscopische colorectale resectie ondergaan. De film is verkrijgbaar in verschillende maten en slechts klevend aan één zijde, wat hem mogelijk geschikter maakt voor plaatsing in kleine ruimtes dan andere membraanbarriers. De primaire uitkomstmaat is de incidentie van adhesies op de plaats van de incisie. Incidentie van adhesies wordt beschouwd als het meest waardevolle surrogaat eindpunt voor klinisch relevante adhesiepreventie, omdat een dunne darmobstructie en adhesiolyse bij reoperatie zeer waarschijnlijk niet zullen optreden wanneer volledige adhesiepreventie wordt bereikt. Deze studie zal waardevolle prospectieve informatie opleveren over adhesieformatie na laparoscopische vergeleken met open colorectale resectie en over de effectiviteit van het gebruik van een adhesiebarrier om adhesies te voorkomen.

Dankwoord

Dankwoord

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Curriculum Vitae

Curriculum Vitae

Martijn Stommel was born on the 1st of August in 1979. He grew up in Tilburg, the Netherlands. After graduating from the Odulphuslyceum in Tilburg in 1997, he took a year for orientation on his plans for the future. During this year he participated as a volunteer in Oyugis Integrated Project in Oyugis, Kenya, where his interest in medicine arose. After a year of Law at the University of Amsterdam, he started Medical School at the Radboud University Nijmegen in 1999. During Medical School he lived at fraternity house Omnivagus and was a member of fraternity Widukind. After graduating from Medical School in August 2005 he started working at the Department of Surgery of Rijnstate Hospital in Arnhem (dr. J.H.G. Klinkenbijl). In July 2006 he started his residency in surgery at the Radboud University Medical Center (prof. dr. R.P. Bleichrodt and prof. dr. H. van Goor), which he continued from July 2009 untill June 2012 at Hospital Gelderse Vallei, Ede (dr. J.H.C. Kuijpers and dr. R.M.H.G. Mollen). During his surgical training Martijn was member of the board of the Association of Surgical Trainees in the Netherlands (VAGH) for two years. In Hospital Gelderse Vallei Martijn was trained as a gastrointestinal and minimally invasive surgeon. After finishing his residency he worked as a surgeon in Hospital Gelderse Vallei for half a year, before starting a fellowship in gastrointestinal-oncological surgery and hepatopancreatiobiliary surgery at the Radboud University Medical Center.

In January 2012 Martijn became interested in the subject of peritoneal adhesions due to a presentation by professor Van Goor on this subject at the Balthasar Gerards Symposium in Delft. Shortly thereafter they made up a research plan, finally resulting in this thesis.

Martijn Stommel is the (co-) author of over 15 peer-reviewed articles. He lives together with Riske Swens and their children Fien and Daan in Nijmegen.